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# STUDIES IN ASYMPTOMATIC NEUROSYPHILIS

## II. THE CLASSIFICATION, TREATMENT, AND PROGNOSIS OF EARLY ASYMPTOMATIC NEUROSYPHILIS *

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The work of many observers during recent years has demonstrated that in a large proportion of all patients who have contracted syphilis the central nervous system is invaded by the Treponema pallidum at the time of its general dissemination in the first months following infection. This invasion is easily detected, in most instances, by early examination of the cerebrospinal fluid. The percentage of patients thus found to have early fluid abnormalities approximates the incidence of late clinical neurosyphilis—one fact which makes it probable that when central nervous system invasion does take place, it practically always occurs during the first months of the infection rather than at some later period. If this viewpoint be accepted, it is essential to examine the conditions under which neurologic invasion may occur. In addition, this paper will discuss the clinical and laboratory methods necessary for its detection, and the response to treatment of these early forms of neurosyphilis.

* This clinical research has been aided by grants from the United States Interdepartmental Social Hygiene Board and from the American Social Hygiene Association.

Leaving out of consideration the occasional precocious appearance of the characteristic late forms of clinical neurosyphilis such as paresis, tabes, etc., we have classified early neurosyphilis appearing within a year or less from the date of infection under five clinical groups:—

1. *Acute syphilitic meningitis*, occurring in previously untreated patients. It may be recognized as syphilitic by the accompanying signs of a recent early syphilis and by the characteristic cyto-biology of the cerebrospinal fluid.

2. *Precocious vascular neurosyphilis*, indicated by transitory aphasia, monoplegia, hemiplegia, etc.

3. *Neurorecurrence*. This type occurs only under definite conditions, *i.e.*, in a patient with early syphilis who has received an amount of treatment insufficient to eradicate the disease, which is then followed by a complete lapse of treatment. The clinical manifestations are varied, but usually consist of a sub-acute meningitis, commonly with, but sometimes without, focal cranial nerve lesions (most often paralyses of the seventh or eighth cranial nerves). Occasionally epileptiform seizures occur.

4. *Neurosyphilis manifested by mild symptoms or slight physical signs, not of themselves diagnostic of central nervous system damage*. Patients in this group may complain of headache, neuralgic pains, insomnia, vertigo, or "nervousness," or may have no symptoms. Those with symptoms may or may not present the minor physical abnormalities which characterize the symptom free group, such as slight pupillary abnormalities (myosis, mydriasis, anisocoria, irregularity, or sluggish light reaction), and exaggeration, sluggishness, or inequalities of the reflexes. These symptoms and signs are not pathognomonic and may occur in non-syphilitic patients.

5. *Asymptomatic neurosyphilis*. The patients in this group have no complaint, and show no physical abnormalities. The neurologic invasion is detected only by examination of the cerebrospinal fluid.

The first two of these five groups, precocious meningeal and vascular neurosyphilis, are rare, and for the purposes of this paper may be disregarded. The group of neurorecurrences has been comprehensively studied by others.[1]

Groups 4 and 5 constitute the largest and most important class of patients. Owing to their minor character, the symptoms and signs detailed under the fourth group may be disregarded for the purpose of discussion, and these two groups considered together under the common name of early asymptomatic neurosyphilis. It will be shown that the recognition of these cases is easily accomplished; that from the ranks of these patients may arise certain of the future outspoken neurosyphilitics;[2] that a study of the spinal fluid abnormalities observed permits a division into three sub-groups; and that the adjustment of treatment to the type of case will usually bring about a clinical and serologic "cure."

This paper is based on the study of 352 patients with primary or secondary syphilis from the Syphilis Department of the Johns Hopkins Hospital. In this series are arbitrarily included those patients whose disease on admission was of less than one year's duration. The available data in all cases consist of anamnesis, careful physical and neurologic examinations, accurate details of treatment, and blood and spinal fluid examinations. The last usually includes cell count, globulin test (Pandy), Wassermann test with 0.2, 0.4, and 1.0 cc. of fluid, with both plain alcoholic and cholesterinized antigens, and colloidal gold and mastic[3] curves. In a few cases cell counts or colloidal tests are lacking. Spinal puncture was performed as a routine after one or two courses of arsphenamin (from two to six months after admission),[4] though in a few cases it was done much earlier or much later in the course of treatment. Puncture before treatment has been considered unjustifiable, partly because of the delay necessary in starting treatment, and partly because of the theoretical danger of transferring organisms from an infected blood stream to a non-infected cerebrospinal axis, either directly through the puncture wound with hemorrhage into the subarachnoid space, or by an alteration of the meningeal permeability.[5]

TABLE I.

The incidence of early neurosyphilis in primary and secondary syphilis.

| | Number | Per cent. |
|---|---|---|
| Total cases | 352 | 100 |
| Acute syphilitic meningitis | 2 | 0.56 |
| Precocious vascular neurosyphilis | 1 | 0.28 |
| Neurorecurrences | 19 | 5.3 |
| Early asymptomatic neurosyphilis | 72 | 20.4 |
| Total early neurosyphilis | 94 | 26.4 |

[1] Zimmermann, E. L.: Neurorecurrences, following treatment with Arsphenamin. Arch. Derm. and Syph., V, 723, (June) 1922. This paper deals with the neurorecurrences observed in this clinic, and contains a thorough review of the literature.

[2] It is recognized that nothing in this paper can be applied to the early detection of purely vascular neurosyphilis. The lesion in this type of case may be a small perivascular infiltration deeply buried in nervous tissue, and inaccessible to early clinical or laboratory methods of detection.

[3] Keidel, A., and Moore, J. E.: Comparative Results of Colloidal Mastic and Colloidal Gold Tests. Arch. Neur. and Psych., VI, 163, (Aug.) 1921.

[4] For five years, spinal puncture has been performed in the outpatient clinic, the patients being instructed to go home to bed for 48 hours. In that period, more than 3000 spinal punctures have been done, with no serious after-results. About half the patients suffer with puncture headache, but this unpleasant reaction is more than counter-balanced by the value of the information gained. Of course, this procedure is not advised if hospital beds are available.

[5] Weed, L. H., Wegeforth, P., Ayer, J. B., and Felton, L. D.: A Study of Experimental Meningitis. Monographs Rockefeller Inst. for Med. Research, No. 12, March 25, 1920.

Ninety-four of the 352 patients developed early neurosyphilis, and are subdivided as shown in Table I. Of these early neurosyphilitics, 76.6 per cent were asymptomatic. The importance of this sub-group is at once apparent.

In a preliminary communication [6] a tentative division of early asymptomatic neurosyphilis into three groups was outlined, the grouping being based in part on the type of spinal fluid abnormalities (in 166 cases), and in part on the response of the various types to treatment. Further observation of this much larger series lends support to this tentative classification, and indicates that an appreciation of the grouping has a real prognostic value.

The first group of this classification includes those cases in which the spinal fluid abnormalities consist of pleocytosis, usually slight,[7] a slight increase in globulin content, but negative Wassermann reaction and colloidal tests (Table II).[8] The discussion of treatment of this and other groups will be deferred till later in the paper, but it may be stated here that routine anti-syphilitic treatment suffices to clear up these abnormalities in practically all instances.[9]

TABLE II.
Spinal Fluid findings of Group I, Early Asymptomatic Neurosyphilis.

| Case | Cells | Glob. | Wassermann | | | Colloidal Gold | Colloidal Mastic |
|---|---|---|---|---|---|---|---|
| | | | 0.2 | 0.4 | 1.0 | | |
| Zx2 | 8 | ± | 0 | 0 | 0 | 1222110000 | 1000000000 |
| Yx11 | 10 | ++ | 0 | 0 | 0 | 2211100000 | 2221000000 |
| Jx20 | 8 | ± | 0 | 0 | 0 | 1122222200 | 2100000000 |
| Hx8 | 13 | ± | 0 | 0 | 0 | 1100000000 | 2210000000 |
| Bx2 | 9 | + | 0 | 0 | 0 | 1122211000 | 2210000000 |
| Fx24 | 8 | ± | 0 | 0 | 0 | 1111100000 | 2210000000 |
| Fx6 | 21 | + | 0 | 0 | 0 | 0011100000 | 2210000000 |
| Ex12 | 18 | ++ | 0 | 0 | 0 | 1222100000 | 2221100000 |
| 20 | 13 | + | 0 | 0 | 0 | 1221000000 | |
| Gx30 | 7 | ++ | 0 | 0 | 0 | 1111100000 | 1110000000 |
| Px21 | 6 | ± | 0 | 0 | 0 | 0111100000 | 2100000000 |
| Nx29 | 20 | + | 0 | 0 | 0 | 1122211000 | 1000000000 |
| Hx28 | 8 | ± | 0 | 0 | 0 | 0000000000 | 2222100000 |
| 6 | 8 | ± | 0 | 0 | 0 | 0011000000 | |
| T16 | 8 | ± | 0 | 0 | 0 | 1221000000 | |
| Lx16 | 15 | + | 0 | 0 | 0 | 0000000000 | 1111100000 |
| M31 | 8 | ++ | 0 | 0 | 0 | 1110000000 | |
| Kx18 | 10 | + | 0 | 0 | 0 | 1100000000 | 1122110000 |

In Group II are included those patients whose spinal fluids show a more marked pleocytosis, with cells between 10 and 100, but usually less than 50; the globulin content also is greater than in Group I; the Wassermann reaction may be either positive or negative, but if positive, fixation usually occurs only with large amounts of fluid; of the two colloidal tests, either or both may be positive, the gold being of the syphilitic zone type, and the mastic curve usually to 3, or rarely paretic. Table III shows the detailed findings in 37 cases. It is apparent that Group II is the most elastic of the three groups.

TABLE III.
Spinal Fluid findings in Group II, Early Asymptomatic Neurosyphilis.

| Case | Cells | Glob. | Wassermann | | | Colloidal Gold | Mastic Colloidal |
|---|---|---|---|---|---|---|---|
| | | | 0.2 | 0.4 | 1.0 | | |
| B4 | 56 | +++ | 4 | 4 | 4 | 1123311000 | |
| C13 | 98 | + | 1 | 3 | 4 | 1234421100 | |
| M18 | 63 | +++ | 4 | 4 | 4 | 1123332100 | |
| Fx14 | 15 | ++ | 0 | 0 | 0 | 0011110000 | 3222000000 |
| Ab14 | 10 | + | 0 | 0 | 0 | 222*32*11000 | 1100000000 |
| Ru | 12 | + | 0 | 0 | 0 | 0112110000 | 3211000000 |
| Sy | 28 | + | 0 | 0 | 4 | 1211100000 | 5543220000 |
| Px22 | 29 | ± | 0 | 0 | 4 | 1111000000 | 2210000000 |
| Gx1 | 3 | +++ | 0 | 0 | 4 | 1111110000 | 3221000000 |
| Ax17 | 21 | ++ | 0 | 0 | 0 | 2445522100 | 2111000000 |
| Ix17 | 14 | +++ | 4 | 4 | 4 | 2222200000 | 4322200000 |
| Ix1 | 2 | + | 0 | 0 | 0 | 1233332000 | 1000000000 |
| Bx29 | 21 | + | 0 | 0 | 1 | 1112333000 | 5432110000 |
| C15 | ? | + | 0 | 0 | 4 | 1234411000 | |
| Mx20 | 6 | ± | 0 | 0 | 0 | 1234411000 | 2210000000 |
| 121 | 16 | ++ | 0 | 0 | 4 | | |
| Kx9 | 14 | + | 0 | 4 | 4 | 1111100000 | 2210000000 |
| Sx12 | ? | ± | 0 | 0 | 4 | 1222100000 | 2210000000 |
| Di | 18 | ++ | 0 | 0 | 0 | 2223222100 | 5543100000 |
| Dm | 16 | ± | 0 | 0 | 0 | 2343100000 | 2211000000 |
| Fx8 | 2 | + | 0 | 0 | 0 | 1211000000 | 3322100000 |
| B19 | 19 | ± | 4 | 4 | 4 | 1222100000 | 5543210000 |
| Zx14 | 12 | ± | 0 | 0 | 0 | 12*33100000 | 2100000000 |
| Fx12 | 2 | ++ | 0 | 0 | 0 | 1111200000 | 3222200000 |
| Kx2 | 24 | + | 0 | 0 | 4 | 0001100000 | 2210000000 |
| Nx27 | 5 | + | 0 | 0 | 0 | 0134211000 | 2000000000 |
| Cx23 | 16 | + | 0 | 0 | 0 | 0123100000 | 4322100000 |
| Fx10 | 8 | ++ | 0 | 1 | 4 | 3433211000 | 5543200000 |
| Bx15 | ? | + | 1 | 4 | 4 | 1123110000 | 3222100000 |
| Jx16 | 2 | ++ | 0 | 0 | 0 | 3333210000 | 3221000000 |
| Px3 | 7 | + | 0 | 0 | 0 | 2332110000 | 3220000000 |
| Px5 | 3 | + | 0 | 0 | 0 | 1133110000 | 3221000000 |
| Dx15 | 40 | +++ | 0 | 0 | 4 | 1123311000 | |
| Dx5 | ? | +++ | 0 | 0 | 0 | 2233100000 | 2220000000 |
| Nx20 | 4 | ++ | 0 | 0 | 0 | 0123322000 | 2210000000 |
| Nx30 | 2 | +++ | 0 | 0 | 4 | 1555555210 | 0033220000 |
| Bb16 | 4 | ± | 0 | 0 | 0 | 443*3321000 | 4321000000 |

[6] Keidel, A., and Moore, J. E.: Studies in Asymptomatic Neurosyphilis:—I. A Tentative Classification of Early Asymptomatic Neurosyphilis. Arch. Neur. and Psych., VI, 286, (September) 1921.

[7] The standard of cell normality has been considered to be from 0 to 5 cells. From 6 to 10 is considered borderline, and such a fluid has not been classed as pathologic unless there was a concomitant increase in the globulin content. More than 10 cells per cu. mm. is definitely abnormal. This standard is based on the work of W. Schönfeld, Ueber Befunde in der Rückenmarksflüssigkeit bei nervengesunden Menschen. Deutsche Ztschr. f. Nervenh., LXIV, 300, 1919.

[8] No stress is laid on alterations in pressure or on the isolated presence of a small amount of globulin, since both of these are frequently found in normal individuals. Both colloidal curves have been classed as negative if there was no change reading higher than 2.

[9] Justification for regarding these spinal fluid changes as evidence of neurologic damage is given by O. Fischer, (Die Anatomische Grundlage der Cerebrospinalen Pleozytose. Monatschr. f. Psych. u. Neur., XXVII, 512, 1910).

and that certain cases fall into this group, instead of into Groups I or III, only because of the results of the colloidal tests. It is for this reason that we do not consider a fluid examination complete, unless at least one and preferably both of the colloidal tests can be performed. In this group also a serologic and clinical "cure" [10] may be obtained by slight modifications in the usual routine of anti-syphilitic treatment without the addition of intraspinal therapy.

Group III includes those cases in which the spinal fluid changes are of a more advanced type. The cell count is high, ranging from 50 to 200. The globulin content is markedly increased; the Wassermann reaction is positive with small amounts of fluid (0.2 cc. or less); and the colloidal gold and mastic curves are both paretic (Table IV). The abnormalities of this group are much more

TABLE IV.

Spinal Fluid findings in Group III, Early Asymptomatic Neurosyphilis.

| Case | Cells | Glob. | Wassermann | | | Colloidal Gold | Colloidal Mastic |
|---|---|---|---|---|---|---|---|
| | | | 0.2 | 0.4 | 1.0 | | |
| 11 | 32 | +++ | 4 | 4 | 4 | 5554310000 | |
| 13 | 91 | ++++ | 4 | 4 | 4 | 5555540000 | |
| 77 | 58 | ++++ | 4 | 4 | 4 | 5552110000 | |
| 90 | 68 | ++ | 4 | 4 | 4 | 5555431000 | |
| O1 | 12 | +++ | 4 | 4 | 4 | 5555321000 | |
| X4 | 64 | ++ | 4 | 4 | 4 | 5555542000 | |
| S32 | 18 | +++ | 4 | 4 | 4 | 5554210000 | |
| S47 | 28 | ++ | 4 | 4 | 4 | 5555553100 | |
| Gx18 | 42 | +++ | 4 | 4 | 4 | 5555533200 | 5543210000 |
| Hx5 | 65 | ++++ | 4 | 4 | 4 | 2211000000 | 5543210000 |
| Jx1 | 98 | +++ | 4 | 4 | 4 | 5555543000 | 5532100000 |
| Qx27 | 150 | ++++ | 4 | 4 | 4 | 5555442100 | 5555542100 |
| Du | 112 | +++ | 4 | 4 | 4 | 5441100000 | 5532100000 |
| Mo | 156 | ++++ | 4 | 4 | 4 | 5555520000 | |
| Ze | 131 | ++++ | 4 | 4 | 4 | 5555554100 | |
| Br | 37 | ++++ | 4 | 4 | 4 | 5555521000 | |
| Ho | 40 | ++++ | 4 | 4 | 4 | 5555421000 | |

resistant to treatment than the preceding two; and practically no improvement results from the routine use of arsphenamin and the mercurials. Intraspinal therapy as an adjunct to routine treatment offers almost the only chance of a serologic cure.

The relative incidence of these three groups is shown in Table V. Of 67 patients with primary syphilis, 20.9 per cent had abnormal fluids (9.1 per cent fluid abnormalities in sero-negative, 26 per cent in sero-positive, primary syphilis). In the 263 patients with secondary syphilis, 22.1 per cent of the fluids were abnormal. If argument for the early diagnosis and vigorous treatment of primary syphilis were needed, it would be furnished by these figures; although it is evident that in some instances neurologic invasion may occur no matter how early treatment is begun.

TABLE V.

Incidence of early asymptomatic neurosyphilis in primary and secondary syphilis.

| | Total | Normal | Abnormal | Fluids falling into Groups | | |
|---|---|---|---|---|---|---|
| | | | | I | II | III |
| Primary | 67 | 53 | 14 (20.9%) | 3 | 9 | 2 |
| Secondary | 263 | 205 | 58 (22.1%) | 15 | 28 | 15 |
| Total | 330 | 258 | 72 (21.8%) | 18 | 37 | 17 |

Under the conditions of this study (examination of the spinal fluid after a considerable amount of treatment) it appears that in Group II we have the most frequent type of abnormal fluid. Of 72 cases of asymptomatic neurosyphilis, 25 per cent fall into Group I; 51.3 per cent into Group II; and 23.6 per cent into Group III. From the reports of other workers [11] on patients with untreated syphilis, it would seem that the minor abnormalities of Group I are much more frequent. Treatment, as we have employed it, may be considered to have accomplished either one or both of two things:—a rapid disappearance of the Group I changes, so that when examined the fluid appears normal; or the opposite effect of intensifying the minor abnormalities, so that a patient who might belong to Group I before treatment falls into Groups II or III after treatment. This assumption, for which some proof exists, constitutes an additional reason to the two already given for delaying puncture until after the administration of anti-syphilitic treatment.

The most important problems in the present day study of neurosyphilis concern the time and manner of invasion of the central nervous system. The scientific aspect of the latter is overshadowed by the practical importance of the former. If it were possible to be reasonably sure of the time limits within which neurologic invasion might occur, the prevention of clinical neurosyphilis by means of its early detection would rest on firmer ground. The best available method of approach to this problem is by a study of the incidence of spinal fluid abnormalities at varying intervals after infection. If invasion of the nervous system occurs within the first months of the infection, one would expect a gradually increasing incidence, reaching a peak during the first or second years, and thereafter remaining at approximately the same

[10] The word "cure" is here and elsewhere in this paper used to mean that the patient remains clinically well, and that the serology of the blood and spinal fluid becomes negative and remains so for the period of observation. It is not used in the sense of eradication of the last remaining organism. Hereafter, the quotation marks will be dispensed with.

[11] Particularly G. L. Dreyfus, (Münch. Med. Woch., LXVII, 1369, 1920) who finds from 70 to 80 per cent of abnormal fluids in untreated secondary syphilis. See also U. J. Wile, and C. K. Hasley: Involvement of Nervous System during Primary Stage of Syphilis, Jour. Am. Med. Assn., **76**, 8, (Jan. 1) 1921.

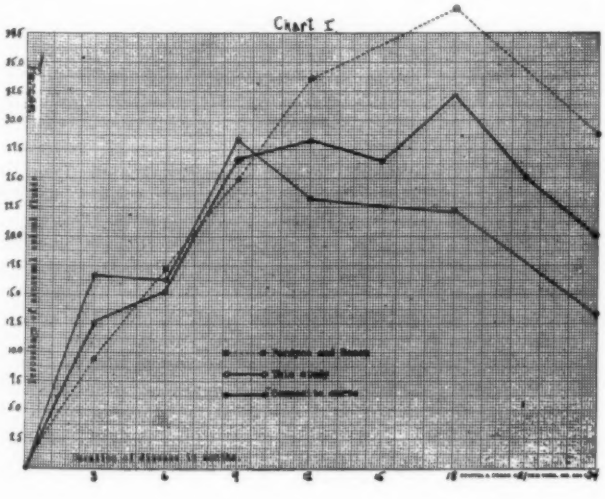
TABLE VI.

The Incidence of Abnormal Spinal Fluids in Primary and Secondary Syphilis, showing the duration of infection in months at the time of puncture:—a comparative study.

| Duration of syphilis in months | Fordyce and Rosen | | | This study | | | Composite results | | |
|---|---|---|---|---|---|---|---|---|---|
| | Normal fluids | Abnormal fluids | Per cent abnormal | Normal fluids | Abnormal fluids | Per cent abnormal | Normal fluids | Abnormal fluids | Per cent abnormal |
| 0—3 | 20 | 2 | 9.0 | 15 | 3 | 16.6 | 35 | 5 | 12.5 |
| 4—6 | 43 | 9 | 17.3 | 37 | 7 | 15.9 | 90 | 16 | 15.1 |
| 7—9 | 30 | 10 | 25.0 | 25 | 10 | 28.5 | 55 | 20 | 26.6 |
| 10—12 | 29 | 15 | 34.1 | 36 | 11 | 23.4 | 65 | 26 | 28.5 |
| 13—15 | 19 | 13 | 40.6 | 42 | 12 | 22.2 | 36 | 13 | 26.5 |
| 16—18 | | | | | | | 25 | 12 | 32.4 |
| 19—21 | 38 | 15 | 28.5 | 34 | 5 | 12.8 | 24 | 8 | 25.0 |
| 22—24 | | | | | | | 48 | 12 | 20.0 |

level. If, on the contrary, this invasion may take place at any time, the curve of incidence should be a constantly increasing one.

In Table VI and Chart I, we have compared the results obtained by Fordyce and Rosen [12] in 243 cases with 237 comparable cases from the present study, and each of these results with a combination of the two series. These patients were all punctured within the first two years of the disease, and the cases are divided into three month periods, showing the duration of infection at the time of puncture. The conditions as to treatment are similar in the two series of cases:—in each instance puncture was deferred until after some treatment, usually one or two courses. The graphic presentation in the chart shows a rapid rise in the incidence of abnormal spinal fluids, which, according to Fordyce and Rosen, reaches its peak




18 months after infection; according to the present series this peak is reached by the ninth month. A consolidation of the two series provides an intermediate curve, probably more accurate than either alone because of the larger number of cases, in which the first peak is reached at the end of 12 months. Thereafter, except for a secondary rise at the eighteenth month, the incidence of abnormalities remains at about the same level. This is further shown in Table VII, in which our own cases are arranged according to the duration of the disease in years at the time of spinal puncture. If the probable statistical error is taken into account, there is little or no variation

TABLE VII.

Incidence of spinal fluid abnormalities, arranged according to the duration of infection in years.

| Year | Total fluids | Normal | Abnormal | Per cent abnormal | Fluids falling into Groups | | |
|---|---|---|---|---|---|---|---|
| | | | | | I | II | III |
| 1 | 149 | 99 | 35 | 23.3 | 11 | 17 | 7 |
| 2 | 95 | 69 | 19 | 20.0 | 4 | 9 | 6 |
| 3 | 27 | 20 | 7 | 25.9 | 1 | 5 | 1 |
| 4 | 28 | 20 | 8 | 28.5 | 2 | 2 | 4 |
| 5 | 19 | 16 | 3 | 15.7 | 1 | — | 2 |
| 6 | 9 | 8 | 1 | 11.1 | — | 1 | — |

[12] Fordyce, J. A. and Rosen, I.: Laboratory Findings in Early and Late Syphilis:—a Review of One Thousand and Sixty-Four Cases. Jour. Am. Med. Assn., 77, 1696, (Nov. 26) 1921.

in the different years. [13] These results are somewhat complicated by the amount of treatment administered, as in general those patients whose disease at the time of puncture was more than two years old had received more treatment than the remainder. This factor may account for the slightly lower percentages in the later duration groups.

Recent experimental work on syphilis has provided information regarding the course of the infection on which an interpretation of these results may be based. Within a few days after infection Treponema pallidum may be recovered from the lymph glands [14] and from the heart's blood of experimental animals.[15] In human syphilis the blood is infectious during the primary and secondary stages, though organisms are probably present only in small numbers. When the period of latency has been reached, it is non-infectious except in rare instances.[16] From the lymph glands, on the contrary, virulent organisms may be recovered at any time during the course of the disease. This has been interpreted to mean that the lymph nodes function as reservoirs for the organisms.

It is probable that at the time of infection, dissemination of organisms takes place from the lymphatic system to the peripheral blood stream. The blood is not an ideal medium for their growth or continued residence, and as soon as possible, they leave it for more favorable surroundings. After a second period of incubation in their new locations, the tissues react with the secondary outbreak. At this time, it is probable that an immune reaction takes place,[17, 18] so that with the spontaneous regression of secondary lesions, the vast majority of the organisms are destroyed by the natural defenses of the body. This reaction may permit the destruction of any further organisms which may be discharged from the lymphatic system to the blood; or the actual discharge may perhaps be prevented by the local tissue reaction in the lymph glands, walling off the organisms and obstructing their egress. When this has been accomplished, the appearance of lesions of the secondary type ceases and latency ensues. The length of time necessary to bring about this result probably varies from three to twelve months.

If, during the first months of the disease, organisms are more or less constantly present in the blood, it is difficult to understand how invasion of the nervous system fails to occur. Evidence is gradually accumulating to show that such an invasion does take place in the majority of all cases,[19] probably by vascular involvement of the meninges, parenchyma, or both. Whether or not clinical neurosyphilis will develop must partially depend on the extent to which the individual patient reacts against his infection.[20] That most patients do succeed in dealing spontaneously with this neurologic invasion is evidenced by the comparatively small number of clinical neurosyphilitics.

The presence of spinal fluid abnormalities may depend on the length of time the organisms have been resident in nervous tissue. If puncture is performed at about the time that invasion occurs, the fluid may be normal, whereas if it had been delayed a few weeks or months, during which the nervous tissues had time to react, definite abnormalities might be present. For example, it is shown by the study of untreated sero-negative primary,

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[13] Moore, J. E.: The Cerebrospinal fluid in Treated Syphilis. Jour. Am. Med. Assn., **76**, 769, (March 19) 1921. A study of 451 cases of late (tertiary and latent) syphilis without neurologic abnormalities showed no higher incidence of abnormal spinal fluids than in early syphilis. The conclusion was drawn that "after the disease is presumably well intrenched, about the same relative number of patients show spinal fluid abnormalities, no matter how long the disease has existed, or by what lesions it manifests itself."

[14] Pearce, L. and Brown, W. H.: A Study of the Relation of Treponema pallidum to Lymphoid Tissues in Experimental Syphilis. J. Exp. Med., XXXV, 39, (Jan.) 1922.

[15] Brown, W. H. and Pearce, L.: A Note on the Dissemination of Spirochæta pallida from the Primary Focus of Infection, Arch. Derm. and Syph., II, 470, (Oct.) 1920. Also Eberson, F.: Dissemination of Spirochæta pallida in Experimental Syphilis, Arch. Derm. and Syph., III, 111, (Feb.) 1921.

[16] Engman, M. F. and Eberson, F.: A Biologic Study of Latency in Syphilis. Arch. Derm. and Syph., III, 347, (April) 1921. This article contains a review of the literature on the infectivity of body fluids.

[17] The question of immunity in syphilis is still *sub judice*, but enough clinical and laboratory evidence exists to make certain the presence of a defensive reaction to infection. The nature of this reaction is as yet unknown. For a discussion of this point, see the article by Engman and Eberson, (footnote 16).

[18] Brown W. H. and Pearce, L.: The Resistance (or Immunity) Developed by the Reaction to Syphilitic Infection. Arch. Derm. and Syph., II, 675, (Dec.) 1920. Experimental Production of Clinical Types of Syphilis in the Rabbit. Arch. Derm. and Syph., III, 254, (March) 1921.

[19] This statement is based on the high percentage of abnormal spinal fluids found by various workers in untreated early syphilis, and on the demonstration of treponemes in the spinal fluid of early syphilitics with otherwise normal fluids. This has been accomplished by Marinesco and Minea (Acad. de Sc., Sem. Méd., 1914, p. 357), Steiner (Neurol. Centralb., 1914, XXXIII, 132), and others. Brown and Pearce have demonstrated organisms in the spinal fluid of recently infected rabbits.

A. Steiner, (Moderne Syphilisforschung und Neuropathologie. Arch. f. Psych., 1913, LII, 1), found pathologic alterations attributable to syphilis in the nervous systems of 16 of 31 rabbits. Six of 8 animals with generalized syphilis showed central nervous system involvement.

[20] It has been suggested, on the theory of immune reactions which may vary in different body tissues, "that all tissues are not equally protected by the general reaction which occurs during the early stages of a syphilitic infection, and that certain tissues which fail to receive this protection, although less susceptible to injury or infection than other tissues, may be capable of only a slight degree of self-protection. This is undoubtedly the case in the experimental animal, and if similar conditions obtain in man, such conditions as neurosyphilis might be explainable on this basis." Brown, W. H. and Pearce, L.: Arch. Derm. and Syph., March, 1921, III, 254.

sero-positive primary, and secondary syphilis, that the incidence of fluid abnormalities rises with a ratio for these examples of about one to three to four, in the order named.[21] This factor must also be considered in connection with the grouping outlined in this paper. A patient classed in Group I, if punctured three months after infection, might fall into Groups II or III if the fluid were studied six months later. The optimum time for the detection of the largest number of cases with abnormal fluids, provided no treatment were administered, would doubtless be from the twelfth to the eighteenth month after infection (see Chart I). The influence of anti-syphilitic treatment, however, makes this delay unnecessary. If treatment is regular and adequate, the abnormalities already present (except for Group III) will rapidly disappear, and opportunity for further neural invasion will be prevented. On the other hand, if a small amount of treatment is followed by a lapse, there is, as will be shown, an increased liability to neurosyphilis. Puncture should be employed as a routine measure, therefore, in all patients with early syphilis at the end of the first or second course of regular treatment. If the fluid is completely negative at this time, puncture need not be repeated until the completion of treatment and observation. Should a lapse in treatment occur, however, the case should be managed as if it were a fresh infection, and puncture be repeated again following the resumption of treatment.[22]

TABLE VIII.

Arrangement of cases by race and sex.

| | | Total fluids | Normal | Abnormal | Fluids falling into Groups | | |
|---|---|---|---|---|---|---|---|
| | | | | | I | II | III |
| Colored | Male | 72 | 61 | 11 (15.1%) | 4 | 5 | 2 |
| | Female | 51 | 43 | 8 (15.6%) | 4 | 4 | — |
| | Total | 123 | 104 | 19 (15.4%) | 8 (6.5%) | 9 (7.3%) | 2 (1.8%) |
| White | Male | 145 | 109 | 36 (24.8%) | 5 | 21 | 10 |
| | Female | 62 | 45 | 17 (27.4%) | 5 | 7 | 5 |
| | Total | 207 | 154 | 53 (25.6% | 10 (4.8% | 28 (13.5%) | 15 (7.2%) |
| Males both races | | 217 | 170 | 47 (21.6%) | 9 (4.1%) | 26 (11.9%) | 12 (5.5%) |
| Females both races | | 113 | 88 | 25 (22.1%) | 9 (7.9%) | 11 (9.7%) | 5 (4.4%) |

It is now necessary to consider other factors which may influence invasion of the central nervous system. In Table VIII the available data are rearranged by race and sex. There is evident a wide difference between the colored and the white races in their susceptibility to early neurosyphilis, the incidence being 15.4 per cent as compared with 25.6 per cent. Cases of the Group I type are about equally frequent in the two races, but Group II is almost twice as common in whites and Group III four times as common. In other words, the negro is not only less prone to neural invasion than the white, but when his central nervous system is invaded, his defensive reactions enable him to deal with the infection so that, judging from the spinal fluid changes, his neurosyphilis is consistently milder than is that of the white. This observation is in accord with statistical data regarding the comparative incidence of paresis and tabes, which are rare in the colored race.[23]

No difference is apparent between the sexes, of either or both races. Early neurosyphilis is as common in women as in men, and the incidence of the various groups is approximately the same. This is a surprising result, in view of the fact that in 763 unselected cases of clinical neurosyphilis, there were four times as many men as women (paresis five times, tabes six times, and cerebrospinal syphilis about three times as frequent). The

TABLE IX.

Showing the incidence of spinal fluid abnormalities according to the age at the time of infection.

| Age group | Total cases | Negative | Abnormal | Per cent Abnormal |
|---|---|---|---|---|
| 0—15 | 4 | 4 | — | — |
| 16—20 | 67 | 55 | 12 | 17.8 |
| 21—25 | 105 | 80 | 25 | 17.9 |
| 26—30 | 77 | 60 | 17 | 22.0 |
| 31—35 | 48 | 35 | 13 | 27.0 |
| 36—40 | 10 | 9 | 1 | 10.0 |
| 41—65 | 19 | 15 | 4 | 21.0 |
| 0—30 | 253 | 199 | 54 | 21.3 |
| 31—65 | 77 | 59 | 18 | 23.3 |

[21] With, C.: Studies on the Different Reactions in the Cerebrospinal fluid in Cases of Syphilis. Brain, 1918, XL, 403. Wile, U. J. and Marshall, C. H.: A Study of the Spinal Fluid in One Thousand Eight Hundred and Sixty-Nine Cases of Syphilis in all Stages. Arch. Derm. and Syph., March, 1921, III, 272.

[22] Moore, J. E.: The Genesis of Neurosyphilis. Arch. Derm. and Syph., July, 1921, IV, 55.

[23] Zimmermann, E. L.: A Comparative Study of Syphilis in Whites and in Negroes. Arch. Derm. and Syph., July, 1921, IV, 75.

explanation is not apparent, though the influence of pregnancy on the disease [24] may play some rôle.

Table IX shows the incidence of spinal fluid abnormalities of all groups arranged by age at the time of infection. There seems to be no special liability for early neurosyphilis to occur in any particular age group, thus disposing of the often expressed theory that if syphilis is acquired in old age the central nervous system is more liable to invasion than early in life. The variations in age groups in this series are well within the limits of statistical error.

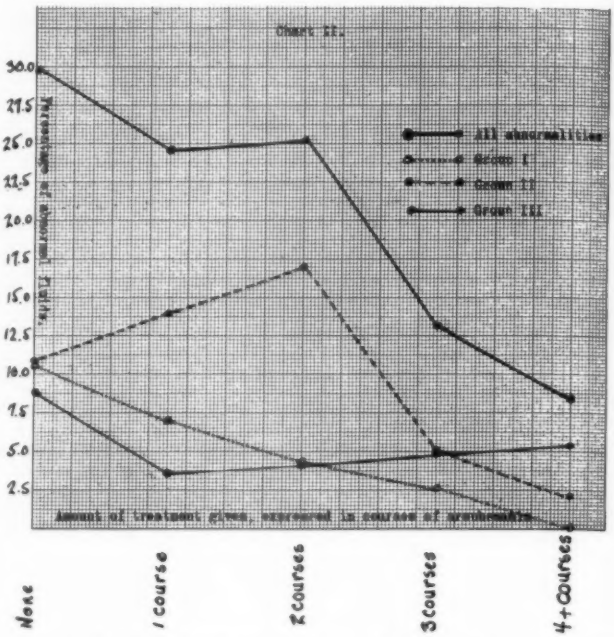
In our preliminary paper [6] it was stated that the incidence of early neurosyphilis was the strongest argument in favor of the adequate treatment of all syphilis, and we presented a series of 151 cases in which the inter-relation of spinal fluid abnormalities and the amount of treatment given prior to the examination of the fluid was studied. The further evidence provided by the present much larger series corroborates our early opinion. These data are shown in Table X and Chart II. Unless treatment is continuous over a comparatively long period of

TABLE X.

Spinal fluid abnormalities in primary and secondary syphilis as influenced by treatment.

| Amount of treatment | Total number of fluids examined | Negative | Positive | Per cent positive | Fluids falling into Groups | | |
|---|---|---|---|---|---|---|---|
| | | | | | I | II | III |
| None or very little | 57 | 40 | 17 | 29.8 | 6 (10.5%) | 6 (10.5%) | 5 (8.7%) |
| Six doses arsphenamin ± mercury | 115 | 87 | 28 | 24.3 | 8 (6.9%) | 16 (13.9%) | 4 (3.4%) |
| Twelve doses arsphenamin plus mercury | 70 | 52 | 18 | 25.7 | 3 (4.2%) | 12 (17.1%) | 3 (4.2%) |
| Eighteen doses arsphenamin plus mercury | 38 | 33 | 5 | 13.1 | 1 (2.6%) | 2 (5.2%) | 2 (5.2%) |
| Twenty-four or more doses arsphenamin plus mercury | 50 | 46 | 4 | 8.0 | — | 1 (2.0%) | 3 (6.0%) |

time, no marked effect is apparent. One or two courses of arsphenamin, with or without mercury, accomplish little. When three courses are given, and particularly if treatment is regular, a decided drop in the incidence of abnormalities occurs; and after four or more courses the




abnormal percentage is very low. Reference to Chart II shows that the number of cases of the Group I type is rapidly decreased by treatment, the fall in percentage being from 10.5 when no treatment or very little is given, to zero when four or more courses are administered. A curious change is seen in the curve for the Group II type. Instead of an early and continuous drop in the incidence of this group, there is a sustained rise from 10.5 per cent, after no treatment or very little, to 13.9 per cent after one course, and to 17.1 per cent after two courses of treatment. At this point the incidence begins to decrease; after three courses it is 5.2 per cent, and after four, 2 per cent. The interpretation of this phenomenon is difficult; but it is probably closely related to the question of the influence of a lapse in treatment in causing the appearance of precocious neurosyphilis. Two probable deductions may be made from this curve:—(1) a number of patients, who, if punctured before treatment, would have shown normal or Group I fluids, later fall into Group II because of the influence of insufficient treatment followed by a lapse. In other words, they represent asymptomatic neurorecurrences, and fail to develop symptoms only because the lesion is in a "silent area," not involving cranial nerves or other important structures;[25] (2) these cases plus the ones originally in

[24] The mild course of syphilis in pregnant women is a well established clinical fact. Experimental evidence of the ability of pregnancy to suppress syphilitic manifestations has been furnished by Brown and Pearce:—On the Reaction of Pregnant and Lactating Females to Inoculation with Treponema pallidum —a Preliminary Note. Am. J. Syph., Oct., 1926, IV.

[25] Gennerich, W.: Die Syphilis des Zentralnervensystems Berlin, Julius Springer, 1921.

Group II are rapidly cleared up serologically after further adequate treatment.

Cases of the Group III type are apparently uninfluenced by treatment, no matter how far prolonged. Their incidence is almost as high following four or more courses of arsphenamin plus mercury as when no treatment at all is given. It is worthy of note, that, as the period of treatment is prolonged, the curve representing that of all abnormalities begins to approach that of the Group III type; so that presumably, if treatment were continued long enough, Groups I and II would disappear, and the Group III curve would replace that for all abnormalities, continuing in approximately a straight line. When the treatment of these three abnormal groups is discussed in detail, evidence supporting these interpretations will be provided.

It is of interest to examine the influence of a lapse in treatment on the incidence of these various abnormal groups.[26] The data on this point are shown in Table XI. Under the heading of "regular" treatment are classed all patients in whom spinal puncture was performed either before any treatment whatever was given, or immediately following the administration of treatment which was carried out in a regular manner. Under the heading "lapsed" are included all patients who, after taking from one to twelve doses of arsphenamin either with or without mercury, voluntarily discontinued treatment and were punctured some weeks, months, or years later. The incidence in the latter class of patients is three times as high as in the former. Still more significant is an analysis of the types of abnormalities found. From this angle the table shows that under the conditions of lapsing treatment, as compared with regular treatment, the percentage of Group I cases is three times as high, of Group II twice as high, and of Group III twelve times as high. It is demonstrated (Table X and Chart II) that regular treatment decreases the incidence of two of these group types. Irregular treatment, on the contrary, not only increases their incidence very markedly, even to a higher percentage than that observed when no treatment at all has been given, but what is much more portentous of gravity in the situation, this faulty management often intensifies the character of the spinal fluid changes. The explanation of this phenomenon is identical with that advanced to account for the mechanism of neurorecurrences.[27]

TABLE XI.

The Effect of a Lapse early in treatment in causing the development of spinal fluid abnormalities.

| Treatment | Total cases | Negative | Positive | Per cent positive | Fluids falling into Groups | | |
|---|---|---|---|---|---|---|---|
| | | | | | I | II | III |
| Regular | 206 | 181 | 25 | 12.1 | 6 (2.9%) | 17 (8.2%) | 2 (0.9%) |
| Lapsed | 124 | 77 | 47 | 37.9 | 12 (9.6%) | 20 (16.1%) | 15 (12.0%) |

The existence of a neurotropic strain of organism as a possible etiologic factor was also investigated.[28] In this series of 72 cases of asymptomatic neurosyphilis it was possible to examine the marital partner by the standards laid down in our first paper (history, physical and neurologic examination, blood Wassermann and a study of the

TABLE XII.

The Incidence of Conjugal Neurosyphilis in the Partners of Asymptomatic Neurosyphilitics.

| Case no. of patient with asymptomatic neurosyphilis | Group | Sex of partner | Partner syphilitic | Partner neuro-syphilitic | Type of neurosyphilis in partner |
|---|---|---|---|---|---|
| 20 | I | M | Yes | No | |
| C 13 | II | M | Yes | No | |
| M 18 | II | M | Yes | Yes | Cerebrospinal syphilis; duration of infection 3 years. |
| Px 22 | II | F | No | No | |
| Gx 1 | II | F | Yes | No | |
| Fx 8 | II | F | Yes | Yes | Asymptomatic neurosyphilis; duration of infection 10 months. |
| Jx 16 | II | F | No | No | |
| D 15 | II | F | Yes | No | |
| 11 | III | M | Yes | No | |
| Hx 5 | III | M | Yes | Yes | General Paresis; duration of infection 12 years. |

[26] Fraser, A. R. and Duncan, A. B. G.: A Possible Explanation of the Increased Incidence and Early Onset of Neurosyphilis. Brit. J. Derm. and Syph., 1921, XXXIII, July, 251; Aug.-Sept., 281.

[27] This reaction is not, as has been assumed by Klauder (Early Neurosyphilis Asymptomatica, Am. J. Syph., 1919, III, 559), a Herxheimer reaction, as we understand the limitations of this term. The Jarisch-Herxheimer reaction follows only the first injection of a series of arsphenamin, occurs within a few hours after the injection, and consists of an acute tissue reaction in a syphilitic lesion due to the rapid destruction of the spirochætes which it contains. The type of response referred to above, on the contrary, occurs in the central nervous system or elsewhere some weeks after the cessation of treatment, the interval being occupied by the multiplication of organisms in the focus and the reaction of the tissues to their presence. The length of time necessary to produce this result corresponds closely with the incubation period of a lesion at the point of first inoculation.

[28] Moore, J. E. and Keidel, A.: Studies in Familial Neurosyphilis:—I. Conjugal Neurosyphilis. Jour. Am. Med. Assn., July, 1921, 77, 1.

cerebrospinal fluid) in ten cases, with positive results in only three. A summary of these data appears in Table XII. Eight of the marital partners of the patients in this series had syphilis; but only three were neurosyphilitic; These were partners of two Group II patients and one Group III patient, respectively. While it is of course recognized that this series is too small to permit any definite conclusions, there is no suggestion that strain of organism is here an important factor.

That many patients with clinical neurosyphilis give a history of very slight or no general manifestations of secondary or tertiary syphilis is a fact beyond dispute.[29] This has led to the conclusion that the greater the early tissue reaction, the smaller the liability to late grave manifestations. In other words, those patients who react to a recent infection with a violent secondary outbreak are assumed thereby to develop a defense, probably of the type of tissue immunity, against later lesions. So far as neurosyphilis is concerned, its lower incidence in the colored as compared to the white race lends some support to this view. It has been frequently shown that secondary syphilis in negroes is more extensive and more severe than in whites. In order to discover if this factor played any rôle in the production of early asymptomatic neurosyphilis, the early lesions of the 72 patients in this series have been studied. It is obviously impossible to decide upon any strict basis of comparison for the extent or severity of early secondary syphilis because of the individual equation of the examiner. We have therefore subdivided the types of early lesions seen into three groups:—mild, average, and severe. Primary syphilis has been considered as mild if there was a single diminutive chancre, or if the proper period for the appearance of secondary lesions was much overdue, and as severe, if there was an extensive single or multiple lesion. Mild secondary syphilis is that manifested by a sparse rash of a macular or papular type, or by a few mucous lesions only; those cases classified as severe were all specifically noted to have very profuse rashes. All other cases are classed as average. On this basis, Table XIII shows that in the 72 early neurosyphilitic patients, mild early manifestations were three times as frequent as in 174 unselected cases of early syphilis, and that this increase takes place at the expense of the average group. It is noteworthy that 13.8 per cent of these neurosyphilitic patients, however, had extensive secondary outbreaks. Although, therefore, failure to react vigorously to a recent infection seems to predispose to neurosyphilis, a violent secondary outbreak does not necessarily protect the patient against it. There is nothing in this fact to strengthen the argument of the advocates of a neurotropic strain of organism.[30]

TABLE XIII.

Character of Early Cutaneous Lesions of Syphilis in Early Asymptomatic Neurosyphilis.

| Group | Total cases | Character of early cutaneous lesions | | |
|---|---|---|---|---|
| | | Mild | Average | Severe |
| I | 18 | 5 | 11 | 2 |
| II | 37 | 15 | 16 | 6 |
| III | 17 | 7 | 8 | 2 |
| Total | 72 | 27 (37.5%) | 35 (48.6%) | 10 (13.8%) |
| Unselected cases of early syphilis | 174 | 23 (13.2%) | 123 (70.6%) | 28 (16.0%) |

As brought out by this and similar studies[31] there are certain clinical aids to the recognition of this type of early neurosyphilis. These are various subjective and objective symptoms, and the behavior of the blood Wassermann reaction. The subjective symptoms consist of headache, which may be quite mild, but is often severe enough to cause the patient sleepless nights; insomnia without headache; a complaint of vague neuralgic pains over the whole body, which resemble the usual prodromata of various acute infections, especially influenza; giddiness, never severe enough to cause staggering gait or falling, and always, in those cases which we have had examined, without objective lesions in the vestibular branch of the eighth nerve; and nervousness. In Table XIV it is shown that about 30 per cent of those patients with abnormal fluids complained of one or more of these symptoms; while similar complaints were found in only 9.7 per cent of those with negative fluids. It is notable

[29] Fournier, A.: (Paralysie Générale et Syphilis. Paris, Masson et Cie., 1905) was able to follow personally the evolution of the disease from chancre to general paresis in 83 cases. Of these, 70 had only a fleeting roseola or mucous patches or alopecia; 8 had moderate secondary lesions; and 3 had tertiary lesions. Two patients showed no specific manifestations except the chancre. On the other hand, of 243 cases of severe secondary syphilis followed for many years, not one showed symptoms of general paresis or tabes.

[30] Indeed, Fournier found (Traité de la Syphilis, Paris, J. Rueff, 1906, vol. II, part I, p. 7) the same phenomenon for tertiary lesions of any type. The figures are as follows: of 2188 cases of all types of tertiarism, 90.9 per cent were preceded by mild, very mild, or no secondary symptoms; 7.2 per cent by a moderate, and 1.8 per cent by a severe secondary outbreak.

[31] Moore, J. E.: The Cerebrospinal Fluid in Treated Syphilis. Jour. Am. Med. Assn., **76**, 769 (March 19) 1921. Fordyce, J. A.: Importance of Recognizing and Treating Neurosyphilis in the Early Period of the Infection. Am. J. Med. Sc., CLXI, 313, (March) 1921. Schou, H. J.: Nervelidesler ved tidling Syfilis og deres Behandling. Hosp.—Tid., LXIII, 57, 1920; abstr. in Med. Abstr. and Rev., IV, 61, (April) 1921.

TABLE XIV.

The Incidence of Neurologic Symptoms and Minor Neurologic Signs in Early Syphilis.

| C. S. F. | Subjective signs | | | Objective signs | | |
|---|---|---|---|---|---|---|
| | Absent | Present | Per cent in which present | Absent | Present | Per cent in which present |
| Negative | 233 | 25 | 9.7 | 235 | 23 | 8.9 |
| Abnormal | 50 | 22 | 30.5 | 54 | 18 | 25.0 |
| Group I | 14 | 4 | 22.2 | 12 | 6 | 33.3 |
| Group II | 28 | 9 | 24.3 | 30 | 7 | 17.9 |
| Group III | 8 | 9 | 52.9 | 12 | 5 | 29.3 |

that more than half of the Group III cases had one or more of these complaints, usually headache.

The objective signs are, in our experience, almost wholly confined to minor pupillary and reflex changes. Careful sensory examinations, comparable to those carried out by some English observers,[32] have not been made. The pupillary changes are all mild in degree, and consist of slight myosis or mydriasis, inequalities, irregularities, or some incompleteness or sluggishness of the direct or consensual light reaction.[33] Occasionally these phenomena have been noted to develop in this class of patients while under observation. The reflex changes are usually confined to the deep reflexes, most commonly the knee and ankle jerks, and consist only of some exaggeration or sluggishness, or more rarely of inequality. Twenty-five per cent of patients with abnormal fluids showed one or more of these neurologic changes; while 8.9 per cent of those with negative fluids showed similar manifestations.

It is obvious that both these subjective and objective signs may, and frequently do, occur in normal non-syphilitic individuals, as well as in syphilitics in whom no other neurologic damage can be demonstrated. Their presence, therefore, is no more than presumptive evidence of the existence of neurosyphilis. But any or all of them, occurring in a syphilitic patient, should direct the suspicions of the examiner toward this possibility.

[32] Head, H. and Fearnsides, E. G.: The Clinical Aspects of Syphilis of the Central Nervous System in the Light of the Wassermann Reaction and Treatment with Neosalvarsan. Brain, XXXVII, 1, (Sept.) 1914. This is a splendid paper which, in this country, has not received the attention it deserves.

[33] Nonne, M.: Uber die Bedeutung der Liquoruntersuchung für die Prognose von isolierten syphilogenen Pupillenstörungen. Deut. Ztschr. f. Nervenh., LI, 155, 1914.

[34] Stokes, J. H. and Busman, G. J.: A Clinical Study of Wassermannfast Syphilis. Am. J. Med. Sc., CLX, 658, (Nov.) 1920.

We have frequently found, as have others,[34] that a persistently positive blood Wassermann reaction could be explained on the basis of neurosyphilis, and have therefore arranged this material to discover if possible the inter-relation of the two factors. On the basis of about 1000 cases of early syphilis, we anticipate an early reversal of the blood Wassermann reaction. As a matter of fact, a permanently negative blood Wassermann occurs by the sixth weekly dose of arsphenamin in the majority of all such cases. If the blood Wassermann is still positive after a second course of arsphenamin plus interim mercury, we begin a careful search for the cause, paying particular attention to the osseous, cardio-vascular, and central nervous systems. Reference to Table XV shows that after one course of arsphenamin without mercury,

TABLE XV.

Spinal Fluid Abnormalities in Primary and Secondary Syphilis as compared with Blood Wassermann Reaction and Treatment.

| | Blood Wassermann Reaction | Total Number fluids | C. S. F. Normal | C. S. F. Abnormal | Per cent abnormal fluids | Fluids falling into Groups | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | I | II | III |
| After one course of treatment | Positive | 32 | 21 | 11 | 34.3 | 5 | 4 | 2 |
| | Negative | 101 | 77 | 24 | 23.7 | 7 | 15 | 2 |
| | Total | 133 | 98 | 35 | 26.3 | — | — | — |
| After two or more courses of treatment | Positive | 17 | 11 | 6 | 35.2 | 1 | 2 | 3 |
| | Negative | 141 | 119 | 22 | 15.6 | 3 | 12 | 7 |
| | Total | 158 | 130 | 28 | 17.7 | — | — | — |

the blood Wassermann remained positive in 21.4 per cent of all cases with negative spinal fluids, while in the group of those with abnormal fluids it was positive in 31.4 per cent. (Naturally, all patients punctured before treatment are excluded from this table.) Expressed somewhat differently, of those patients with a persistently positive blood Wassermann reaction, 34.3 per cent had abnormal fluids, as compared with 23.7 per cent when the blood test had become negative.

After two or more courses of arsphenamin plus mercury, the figures are more impressive. Of 17 cases with a persistently positive blood reaction, 35.2 per cent showed

abnormal spinal fluids, while only 15.6 per cent of the negative blood cases were abnormal in this respect. In other words, 21.4 per cent of the early neurosyphilitics had a blood Wassermann difficult to reduce, whereas this phenomenon was present in only 8.4 per cent of the cases with a negative spinal fluid. These statistics demonstrate that to the list of subjective and objective signs already detailed must be added the factor of a stubborn blood Wassermann reaction; and that this, when present, should at once arouse the suspicion of neurologic invasion.

*The Treatment of Early Asymptomatic Neurosyphilis.*—When the classification of these cases was discussed, it was stated that the grouping was determined as much by the results of treatment of the various groups as by the type of spinal fluid abnormalities. The Group I type, with only minor abnormalities in the fluid, usually yields readily to routine anti-syphilitic treatment, provided this is carried out for a sufficiently long period of time. Unfortunately, too few cases of the present series have been consecutively treated to furnish convincing statistical proof of this point. This statement is, therefore, based on our experience with patients who miss falling into the classification under discussion by virtue of the longer duration of their disease, on the rapidly falling curve of incidence of Group I cases after adequate treatment (see Chart II), and on the evidence of other workers. Not only do these minor abnormalities disappear, but the patients remain clinically and serologically well.

Thirteen patients in our Group II have been under treatment for a sufficient length of time to allow discussion of the results. The essential data are summed up in tabular form (Table XVI) in order to economize space. Of these cases, one (Px 22) has disappeared from observation; the remaining twelve are well after periods of observation ranging from 8 to 36 months after the first discovery of spinal fluid abnormalities. Eight patients have always been, and have remained, symptom-free. In all five instances in which various subjective symptoms were complained of, these rapidly disappeared. Six patients were found to have the minor neurologic changes described, and in five these objective signs have remained unaltered; while in one case (Ix 17), marked exaggeration of all deep reflexes has disappeared, leaving normal reflexes at present. If, as is probable, these slight abnormalities are evidence of beginning anatomical damage, it is not surprising that treatment usually failed to effect their disappearance.

From the standpoint of the blood Wassermann, all patients have been rendered sero-negative and have remained so. The cyto-biology of the cerebrospinal fluid is shown in the table. In most instances there were several examinations of the fluid made, only the last of which is shown. A negative result was often obtained much earlier than appears in the chart. In ten of the thirteen cases, a serologic cure [10] has been obtained. In one instance (B 19) the cyto-biology of the fluid was markedly improved after 15 months' treatment, while in two cases (Px 22 and Kx 9) it was somewhat worse after smaller amounts of treatment. In each of these two cases the treatment given was very scant and was especially deficient in mercury.

The treatment given to all patients in this group, with

TABLE XVI.

The Results of Treatment of Early Asymptomatic Neurosyphilis—Group II.

| Case No. | Duration of disease on admission | Treatment before first spinal puncture. | Lapse in treatment | Interval admission to spinal puncture | First C. S. F. results | | | | | | | Treatment after first puncture | | Last C. S. F. results | | | | | | | Time elapsed since first puncture | Clinical result | Serologic result | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Cells | Glob. | Wa. R. 0.2 | Wa. R. 0.4 | Wa. R. 1.0 | Gold | Mastic | Arsphenamin | Mercury | Cells | Glob. | Wa. R. 0.2 | Wa. R. 0.4 | Wa. R. 1.0 | Gold | Mastic | | | | |
| B 4 | 8 Mos. | 5x0.6 Neo+Hg. | 6 Mos. | 7 Mos. | 56 | +++ | 4 | 4 | 4 | 1123311000 | — | 30x0.4 | 16 Weeks | 1 | + | 0 | 0 | 0 | 1111100000 | 2210000000 | 19 Mos. | Well | Cure | |
| C 13 | 2 Mos. | 6x0.3 | 0 | 1.5 Mos. | 98 | + | 1 | 3 | 4 | 1234421100 | — | 10x0.3 | 16 Weeks | 8 | 0 | 0 | 0 | 0 | 1121100000 | — | 22 Mos. | Well | Cure | |
| M 18 | 11 Mos. | 12x0.3 & 20 wks. Hg. | 0 | 7 Mos. | 63 | +++ | 4 | 4 | 4 | — | — | 32x0.3 | 16 Weeks | 7 | ± | 0 | 0 | 0 | 1111000000 | 2111000000 | 22 Mos. | Well | Cure | |
| Fx14 | 2 Wks. | 6x0.3 | 37 Mos. | 38 Mos. | 15 | ++ | 0 | 0 | 0 | 0011110000 | 3222000000 | 18x0.4 | 18 Weeks | 2 | + | 0 | 0 | 0 | 1112111000 | 2100000000 | 12 Mos. | Well | Cure | |
| Px22 | 5 Mos. | 6x0.3+30 I. M. Hg. | 3 Mos. | 5 Mos. | 29 | ± | 0 | 0 | 4 | 1111000000 | 2210000000 | 12x0.4 | 4 Weeks | 29 | + | 2 | 4 | 4 | 1122200000 | 1000000000 | 4 Mos. | — | Worse | |
| Gx1 | 4 Mos. | 12x0.4+6 wks. Hg. | 0 | 4 Mos. | 3 | +++ | 0 | 0 | 4 | 1111110000 | 3221000000 | 22x0.4 | 8 Weeks | 1 | + | 0 | 0 | 0 | 2211100000 | 2220000000 | 11 Mos. | Well | Cure | |
| Ax17 | 7 Wks. | 24x0.4+22 wks. Hg. | 0 | 11 Mos. | 21 | ++ | 0 | 0 | 0 | 2445522100 | 2111000000 | 14x0.6 (Neo) | 16 Weeks | 4 | ++ | 0 | 0 | 0 | 1121000000 | 2222100000 | 14 Mos. | Well | Cure | |
| Ix17 | 7 Mos. | None | — | 0 | 14 | +++ | 4 | 4 | 4 | 2222200000 | 4322200000 | 24x0.4 | 34 Weeks | 3 | ± | 0 | 0 | 0 | 0222110000 | 2100000000 | 12 Mos. | Well | Cure | |
| Kx9 | 4 Wks. | 6x0.4 | 0 | 1.5 Mos. | 14 | + | 0 | 4 | 4 | 1111100000 | 2210000000 | 10x0.4 | 4 Weeks | 10 | + | 4 | 4 | 4 | 1111100000 | 2210000000 | 4 Mos. | Well | Worse | |
| Da | 10 Mos. | 15x0.3+20 I. M. Hg. elsewhere | 1 Mo. | 0 | 18 | ++ | 0 | 0 | 0 | 2223222100 | 5543100000 | 12x0.4 | 6 Weeks | 6 | + | 0 | 0 | 0 | 1111000000 | 2100000000 | 14 Mos. | Well | Cure | |
| B 19 | 10 Mos. | 6x0.3 | 0 | 1.5 Mos. | 19 | ± | 4 | 4 | 4 | 1222100000 | 5543210000 | 22x0.3 | 20 Weeks | 3 | ± | 0 | 0 | 2 | 1111000000 | 2100000000 | 15 Mos. | Well | Improved | |
| Dx5 | 8 Mos. | 12x0.4+8 wks. Hg. | 6 Mos. | 7 Mos. | 27 | +++ | 0 | 0 | 0 | 2233100000 | 2220000000 | 6x0.4 | 16 Weeks | 3 | 0 | 0 | 0 | 0 | 1222100000 | 2100000000 | 13 Mos. | Well | Cure | |
| D 15 | 13 Mos. | Irreg. Hg. pills 3x0.4 7x0.4 | 6 Mos. | 23 Mos. | 40 | + | 0 | 2 | 4 | 1122000000 | — | 1 I.S. 5x0.4 1 I.S. | 42 Weeks | 1 | + | 0 | 0 | 0 | 1111100000 | — | 30 Mos. | Well | Cure | |

one exception, consisted of alternating courses of arsphenamin and mercury (by inunction), together with large doses of potassium iodide by mouth. The average course of arsphenamin consisted of from 8 to 12 weekly injections instead of the usual six; the interim between courses was from 1 to 4 months, and was occupied by the constant administration of mercury. In only one or two instances were the two drugs used together. Intraspinal treatment was employed in only one case (D 15).

From a study of these results, it is apparent that patients in this group may be maintained clinically well over long periods of time, and that in the majority of instances the blood and spinal fluid serology may be reduced to normal and maintained there by the use of arsphenamin and mercury by the usual routes of administration, without the use of intraspinal therapy. We have so far not encountered a single patient in this group with whom such a result could not be obtained, provided treatment were sufficiently prolonged. It is, of course, probable that more resistant cases will be met with; in that event, if a six months' trial of routine treatment brought about no improvement, we should at once resort to intraspinal treatment as an adjunct.

The cases in Group III present an entirely different picture. The results in 8 cases of this group are presented in Table XVII. Two patients, both of whom were completely asymptomatic at the time of the first spinal fluid examination, have developed clinical neurosyphilis since that date, and in spite of energetic treatment following the discovery of fluid abnormalities. One of these patients is now, five years after his infection, and in spite of 57 intravenous injections of arsphenamin, 11 intraspinal treatments, and a great deal of mercury, a typical dilapidated paretic. In both of these instances, however, a long period of time, punctuated by frequent lapses in treatment, had elapsed since the date of infection. The remainder are clinically well. No patients are serologically negative, though on the average much more treatment has been given than in the Group II cases. Three are moderately improved; two slightly improved, two unchanged; and in one the cyto-biology of the fluid is worse after 33 intravenous arsphenamins than before. Intraspinal treatments were employed in three of these patients, resulting in a marked improvement in two.

The contrast between the results in Group II and in Group III cases is strikingly shown in Table XVIII. Of the former, 76.9 per cent of the patients are clinically and serologically well, as compared to none of the latter. This part of the study offers confirmatory evidence of the interpretation given for Chart II, in regard to the effect of the amount of treatment given on the incidence of the various groups, since in both places it is shown that Group II is readily influenced by treatment, and Group III very little if at all.

These results can be applied to the controversy over intraspinal treatment, and our attitude in regard to it, so far as this type of case is concerned, can be briefly summed up. For cases of the type of Groups I or II, intraspinal treatment is usually not necessary, and, if applied at all, should not be used until the patient has

TABLE XVII.

The Results of Treatment of Early Asymptomatic Neurosyphilis—Group III.

| Case No. | Duration of disease on admission | Treatment before first spinal puncture. | Lapse in treatment | Interval admission to spinal puncture | First C. S. F. results | | | | | | Treatment after first puncture | | Last C. S. F. results | | | | | | Time elapsed since first puncture | Clinical result | Serologic result |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Cells | Glob. | Wa. R. 0.2 | Wa. R. 0.4 | Wa. R. 1.0 | Gold | Mastic | Arsphenamin | Mercury | Cells | Glob. | Wa. R. 0.2 | Wa. R. 0.4 | Wa. R. 1.0 | Gold | Mastic | | | |
| 11. | 8 Mos. | 2x0.3 | 8.5 Mos. | 9 Mos. | 32 | ++++ | 4 | 4 | 4 | 5555321000 | — | 16x0.35 | 14 Weeks | 7 | ++ | 1 | 4 | 4 | 4320000000 | 5443321000 | 20 Mos. | Well | Slightly improved |
| O 1 | 11 Mos. | 4x0.4 elsewhere | + | — | 12 | +++ | 4 | 4 | 4 | 5555431000 | — | 33x0.4 | Practically none | 61 | ++++ | 4 | 4 | 4 | 5544432200 | 5555321000 | 27 Mos. | Well | Worse |
| X 4 | 6 Mos. | 12x0.35+4 wks. Hg. | 6 Mos. | 11 Mos. | 64 | ++++ | 4 | 4 | 4 | 5555431000 | — | 56x0.4 | 36 Weeks | 1 | ++ | 0 | 2 | 4 | 54443000 | 3321000000 | 31 Mos. | Well | Slightly improved |
| J4 1* | 8 Mos. | 3x? elsewhere 12x0.3+10 wks. Hg. | + 30 Mos. | 36 Mos. | 98 | +++ | 4 | 4 | 4 | 5555430000 | 5532100000 | 22x0.4 | 10 Weeks | 70 | ++++ | 4 | 4 | 4 | 5555521000 | 5543210000 | 10 Mos. | Deep reflexes increased | Unimproved |
| Ze 27 | 3 Mos. | 27x0.3 and much irregular Hg. | Frequent | 46 Mos. | 131 | ++++ | 4 | 4 | 4 | 5555554100 | — | 30x0.4 +11 intraspinal treatments. | Continuously for 14 Mos. | 8 | +++ | 4 | 4 | 4 | 5555321000 | — | 14 Mos. | Asymptomatic at first puncture developed G. P. under treatment | Unimproved |
| H | 24 Mos. | 14x0.4. Irregular Hg. | + | 22 Mos. | 40 | ++++ | 4 | 4 | 4 | 55555421000 | — | 23x0.3 7 intraspinal treatments | 20 Weeks | 2 | ± | 0 | 0 | 4 | 1110000000 | — | 24 Mos. | Well | Improved |
| Em. | 11 Mos. | 1x? elsewhere 15x0.3+12 wks. Hg. | + | 10 Mos. | 156 | +++ | 4 | 4 | 4 | 5555520000 | — | 67x0.3 | 80 Weeks | ? | ++ | 3 | 4 | 4 | 5511100000 | — | 36 Mos. | Well | Slightly improved |
| S 32 | 3 Mos. | 12x0.4+8 wks. Hg. | 0 | 5 Mos. | 65 | +++ | 4 | 4 | 4 | 5554210000 | — | 5 intraspinal | — | 12 | ++ | 0 | 2 | 4 | 5555321100 | — | 3 Mos. | Well | Improved |

TABLE XVIII.

Summary of Treatment of Early Asymptomatic Neurosyphilis, Groups II and III.

| | Total cases treated | Lost track of | Clinically well | Developed clinical neurosyph. | Serologic result | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Well | Improved | No change | Worse |
| Group II | 13 | 1 | 12 | 0 | 10 (76.9%) | 1 | — | 2 |
| | | | | | | (23.1%) | | |
| Group III | 9 | 1 | 6 | 2 | 0 | 5 | 3 | 1 |
| | | | | | | (100%) | | |

had a thorough trial of at least six months of routine anti-syphilitic treatment. For the Group III type, it has been shown that routine treatment accomplishes little or nothing. In these cases intraspinal treatment as an adjunct to routine therapy is of value, because it offers almost the only hope of attaining a serologic cure, and because it tends to bring about improvement more rapidly than the routine method alone, thus obviating some of the dangers attending the too prolonged use of arsphenamin[35] and mercury. In a later paper of this series, which will deal with the question of late asymptomatic neurosyphilis, we hope to support our contentions in this respect with additional evidence.

*The Prognosis in Early Asymptomatic Neurosyphilis.*—It has already been suggested that there is probably no hard and fast line to be drawn between our three groups, and that it may be possible for a patient who falls into Group I on early puncture to belong to Groups II or III if puncture had been carried out later. This change in grouping may also be brought about by the factor of insufficient treatment.

It has occurred to us, as well as to others, that it might be possible for the spinal fluid abnormalities of these groups to clear up spontaneously without the influence of treatment, or that patients showing these changes might remain clinically well without developing neurosyphilis.[36] If these two points could be demonstrated, the stress which we lay on early fluid changes would lose much of its emphasis. So far as the spontaneous disappearance of cyto-biologic abnormalities is concerned, we have not had the temerity to allow such patients to go untreated; and we can say only that, on repuncture of those patients who had voluntarily lapsed in treatment, we have never found a negative fluid. On the contrary, in our few examples of this kind, the later puncture has always shown changes of an intenser degree than the first. We should be inclined to admit the possibility of this conception only in the Group I cases, and we should be very diffident of expression even here.

It is not surprising that adequate statistical data regarding the development of clinical neurosyphilis in these asymptomatic patients are lacking in the literature. Only a few years have passed since the importance of early spinal fluid examinations has been appreciated, and in order to provide data of any value, these patients must be continuously followed over a life time. The longest period of time for which we have been able to follow any untreated case is five years. This patient, a Group III case, is apparently well at present, though she refuses to submit to re-examination. So far, no Group I case, treated or untreated, has developed clinical neurosyphilis. Of our 37 Group II cases, one patient (Sy) whose neurologic examination was completely negative at the time of her first puncture, lapsed in treatment for five months. On her return, her pupils which had been normal were now widely dilated, unequal, markedly irregular, and reacted to light only very sluggishly. One Group II patient is dead (lobar pneumonia). The others, so far as is known, remain well. Those with minor neurologic signs have not gotten worse; those without signs have not developed them.

Of the 17 Group III patients, three have developed general paresis, one after a great deal of treatment, and two after long lapses. A fourth patient has developed outspoken neurologic signs which would now easily allow a diagnosis of cerebrospinal syphilis, though no mental changes are evident. The remainder are apparently well.

*The Prophylaxis of Early Asymptomatic Neurosyphilis.*—The evidence regarding the origin of these various types of asymptomatic neurosyphilis may be applied to the formulation of a scheme of treatment for early syphilis calculated to reduce the incidence of neurologic damage. As long as the treatment of the early stages of the disease continued to rest largely in the hands of the general practitioner rather than of the syphilologist, we consider it unnecessary to argue that there should be a fairly rigid outline of treatment applicable to the majority of uncomplicated cases. The attempt to individualize treatment will be productive of far more harm than good.[26] It is not our intention to enter into the details of our plan of treatment of early syphilis, or the factors which led to its adoption, since this will be fully considered in a later communication.[37] It is necessary, however, to point out briefly the essential features of an adequate plan and to indicate the arguments in its favor provided by the data of this paper.

[35] Moore, J. E. and Keidel, A.: Dermatitis and Allied Reactions following the Arsenical Treatment of Syphilis. Arch. Int. Med., XXVII, 716, (June) 1921.

[36] Kalsiki, D. J. and Strauss, I.: The Significance of Biologic Reactions in Syphilis of the Central Nervous System, with Notes on Treatment, especially Intraspinal. Arch. Neur. and Psych., VII, 98, (Jan.) 1922.

[37] Keidel, A., and Moore, J. E.: The Treatment of Primary and Secondary Syphilis. (To be published.)

Anti-syphilitic treatment in early syphilis should be continuous rather than intermittent. There should be no periods of rest between courses of treatment, because of the tendency of lapsed (or irregular) treatment to increase the incidence of spinal fluid abnormalities. In order to accomplish this, arsphenamin and mercury must be used separately. It is probably best to allow a little overlapping, so that the use of mercury is begun just before the last injection of a course of arsphenamin and is kept up until just after the first injection of the next course.[38] There are additional cogent reasons for this method of use of the two drugs, a discussion of which is out of place in this paper.

The most indefinite part of any plan of treatment is the length of time for which it should be continued. Our own routine, at first adopted arbitrarily but now justified by the data of Table X and Chart II, has been to treat early syphilis continuously until completely negative serology of the blood and spinal fluid has been obtained, and for one full year thereafter. While it is true that some patients will be cured with less than this amount of treatment, it is equally obvious that others will not be cured; and there is at present no means of an early separation of the two groups. The only safe plan, therefore, is to treat all patients up to the point of cure of the majority.

In early syphilis, treatment is begun with arsphenamin, the first course being of eight doses and succeeding courses of six doses each. Mercury by inunction is started just before the last dose of each arsphenamin course, and continued until the first dose of the next. The interval between arsphenamin courses is at first short (four weeks), and is gradually lengthened with each course. The longest interval permitted is twelve weeks. Spinal puncture is performed as a routine after the first or second courses of arsphenamin. If the standard of serologic cure mentioned above is adhered to, the treatment of sero-negative primary syphilis will usually last exactly one year, and will consist of at least 4 courses (26 doses) of arsphenamin and 26 weeks of mercury. In sero-positive primary and in secondary syphilis, the length of treatment in the average case is usually 15 months (5 courses of arsphenamin and 32 weeks of mercury). If spinal fluid abnormalities are found at the time of the first puncture, this plan is modified according to the group of abnormality present. When treatment has been completed, there ensues a year of probation, during which there must be no symptoms, no positive and at least six negative Wassermann tests (ice-box); and, at the end of the year, negative physical and neurologic examination, negative X-ray of the cardio-vascular stripe, and negative examination of the spinal fluid.

[38] Stokes, J. H.: The Applications and Limitations of the Arsphenamins in Therapeutics. Arch. Derm. and Syph., II, 303, (Sept.) 1920.

If this plan of treatment could be applied to every case of primary and secondary syphilis, the incidence of asymptomatic neurosyphilis, and in all probability that of clinical neurosyphilis, might be reduced to an absolute minimum. Judging from the data supplied by this paper, the present level of 20 to 25 per cent of clinical neurosyphilis might be reduced to 5 per cent or less. The economic saving to the state, to mention only one of the advantages of this reduction, would be enormous.

## SUMMARY AND CONCLUSIONS

1. It has been shown that early invasion of the central nervous system in syphilis, is common, occurring in 26.4 per cent of a series of 352 patients with primary and secondary syphilis. Of 94 early neurosyphilitics, 72 were asymptomatic, and were detected only by the routine application of spinal puncture.

2. Early asymptomatic neurosyphilis may be divided into three sub-groups on the basis of the spinal fluid findings and the response of the various groups to treatment.

3. Invasion of the central nervous system probably occurs in the majority of all patients with syphilis, and unless the course of the disease is influenced from without (by treatment), this invasion takes place in most instances within the first year after infection. The ability of the invading organisms to produce clinical neurosyphilis probably depends on the defense mechanism of the individual patient. The experimental and clinical evidence bearing on these points are reviewed.

4. Early asymptomatic neurosyphilis is more common in the white race than in negroes, but is equally frequent in men and women, of either or both races.

5. Prolonged regular treatment influences favorably the incidence of early asymptomatic neurosyphilis. Irregular or lapsing treatment, on the other hand, markedly increases its incidence.

6. A study of this material from the standpoint of strains of Treponema pallidum furnishes no support to the theory of the existence of a neurotropic strain of organism.

7. That the spinal fluid abnormalities of early asymptomatic neurosyphilis are evidence of actual anatomical damage to the nervous system, is indicated by the frequency of certain minor subjective and objective neurologic signs in this class of patients. An appreciation of these signs, and of the significance of a persistently positive blood Wassermann reaction in treated patients, furnishes a clinical diagnostic aid for the recognition of neurologic invasion.

8. Spinal puncture is an indispensable routine procedure in the management of early syphilis. Unless it is employed, many patients will be discharged as cured who are nevertheless candidates for clinical neurosyphilis. It should be performed as a routine after the first or second course of arsphenamin, and unless a lapse in treatment

occurs, need not be repeated (if negative) until the end of treatment and the probation period.

9. All three groups of asymptomatic neurosyphilis may be serologically and clinically "cured" by appropriate methods of treatment.

10. Early asymptomatic neurosyphilis is the forerunner of clinical neurosyphilis. One patient of our second group has developed clinical cerebrospinal syphilis. Of the third group, three patients have developed general paresis and one cerebrospinal syphilis.

11. There is suggested an outline of treatment for early syphilis, the uniform application of which will markedly reduce the incidence of asymptomatic neurosyphilis, and probably, therefore, of clinical neurosyphilis.

# THE BIOCHEMISTRY OF TUBERCULOSIS*

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In the biochemistry of an infectious disease two series of metabolism are naturally concerned, that of the invading parasite, and that of the host as modified by the former's action. The manifestations of disease may be looked upon as alterations in the physiology of the host initiated by the metabolism of entering bacteria, although sometimes no more than initiated, since the bacterial growth may serve to fire a train of subsequent events largely non-specific in character.

There is a natural tendency to think of bacterial cells as simple forms of life, and to a certain extent they are, being largely independent of each other, devoid of that correlation so conspicuous in the physiology of higher forms. But, cell for cell, their life processes are probably fully as complicated as those of a liver or kidney cell, or perhaps even one of the central nervous system. They digest their food, build up complex substances from simple ones, they respire, that is to say, take up oxygen and give off carbon dioxide, they excrete waste products, and they reproduce. And if they are shut off from an adequate supply of nutrition, like other cells they die and tend to autolyze.

Leaving out of present consideration those remarkable forms which snatch nitrogen out of the atmosphere, heap up mountains of sulphur, or spread vast marshes with iron, we have an almost endless variety of microörganisms whose methods of obtaining energy and manner of excreting waste are closely akin to those of cells of highly organized life. Some of these are very adaptable, wonderfully equipped foragers, not overly particular, within reasonable limits, about the temperature at which they work or the form in which the great classes of food-stuffs are supplied to them. They grow in relatively large masses, many dying that others may live, and in their process of dissolution many kinds of them liberate powerful ferments which make more food available for the rest. In view of their relation to organic decay they have received the name of "saprophytes." Etymologically they are decay-growers. They live their day, grow, die and decay themselves, and by virtue of their involuntary sacrifice serve the high purpose of maintaining those great cycles of the elements in which a certain amount of carbon, nitrogen and sulphur is continually available in a mobile state suitable for the nutrition of other forms.

Not all bacteria by any means are so useful as these great cycle maintainers. Not a few, evolutionary accidents in the mighty, invisible struggle for the survival of the fittest, must eke out a more or less miserable existence, dependent for their nurture largely upon the unwitting, lavish generosity of the great hosts of proteo-, lipo- and cellulo-clastic forms, or upon the less willingly provided maintenance of more highly organized life.

Of this last set a certain number have acquired what amounts in the end to a protective adaptation, the mysterious condition of parasitism. This mode of existence, the factors of which were so clearly defined in a recent address by Theobald Smith, has for its essential elements the ability on the part of invading microörganisms to multiply within the tissues of a living being, and to multiply in such place and manner that an easy exit is afforded, from which some of the invaders may escape to another host of the same sort. Thus parasitism as a permanent mode of life necessarily involves a cycle including more than the mere ability to multiply in tissues.

It is, however, only to the first of these factors of parasitism that I shall now make reference, limiting my remarks to the special case of multiplication within the tissues of the human host. The remarkable thing is not that there are so many organisms that possess this capacity, but that there are so few, and that those bacteria which have adapted their nutritional requirements to the difficult conditions obtaining within the host, should be so helpless in the region of bounteous plenty outside, while those which attack dead organic material so energetically seldom establish a home beyond the first barrier of living cells. The typhoid bacillus pursuing its increasingly lonely way down densely populated sewer pipes is a pitiful object beside the infinitely

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more vigorous proteus family; so poorly equipped for the journey is it that after five or six days few members of its group survive to tell of a different phase of their existence, the tale of deadly destruction wrought so short a time before in an environment impregnable to the surrounding billions of saprophytes.

Among these bacteria which, so far as I can see, serve no useful purpose in the great scheme of life, is a group of organisms characterized by the protoplasmic possession of a large amount of non-saponifiable lipoid, which so modifies their reaction to some of our chemical reagents that they can be readily picked out from the rest by a simple application of appropriate stains. This is the acid-fast group. Within it are several varieties, including parasites adapted to life in different hosts, namely, the tubercle bacilli, and saprophytes unable to maintain such existence, although flourishing more or less widely outside.

Time does not permit us to puzzle long over the evolutionary relationship of these forms, but that there is a relationship, remote though it may be, is at least suggested by certain facts. The most outstanding of these is their interchangeability as antigens in the so-called biological reactions, which indicates, according to the more general concepts of immunology, that they possess in common certain proteins, specific to the degree that they are present in no great concentration, or not at all, in the bodies of other bacteria. The "tuberculin," if I may use the term, formed by the growth of a grass bacillus in bouillon, will elicit a typical reaction in a tuberculous animal, as the similar product from a hay bacillus will not, and there seem to be more investigators who believe in a common "acid-fast fixation of complement" than who do not. This refers to qualitative conditions and does not mean that the organisms of the group may not be separated by biologic tests made on a careful quantitative basis.

Certainly these organisms are closely enough allied in their chemical makeup so that it would be difficult or almost impossible to distinguish them as dead chemical material. Give a man an autoclaved culture of grass bacilli and one of tubercle bacilli and he would be a keen analyst if he could distinguish between them. He might filter them off and stain them, noting that they were resistant to acid decolorization, and he might extract them with chloroform and find a content of waxy substances in the neighborhood of 30 per cent, and be able to say, "These are not hay bacilli or typhoid germs; they belong to the acid-fast group." He might go further and make emulsions of the dead bacteria and test them out against tuberculous guinea-pigs by skin inoculation, and confirm his previous conviction on the group to which the organism belonged, and he might perhaps notice that one of his preparations brought out a distinct reaction in quantities definitely less than those required with the other, but he would be fortunate if he could be sure.

It is only with the living material that he could stand up without fear and say, "These are tubercle bacilli, and these are something else in the acid-fast group." And he would have one or perhaps two lines of fire on which he could hit his mark. The first of these would be the establishment of the condition of parasitism in an appropriate host. The second would be the proof of a characteristically different metabolism in non-living culture media. Of these the first would be a bull's-eye, made on a shot through the dark. The second would be made through the light, in so far as known chemical reagents are clear to our understanding, as a guinea-pig is not, but it would probably not be a bull's eye—at present at least. I am convinced that a time will come when a relation of virulence to metabolic activity will be established, but little progress has been made to date. So far as I know, the surest chemical criterion at present for a tubercle bacillus is that discovered by Nocard thirty-five years ago, its marked glycerophilism. Our hypothetical solver of bacteriological unknowns could, I believe, find that for one of his strains glycerol was a practical necessity, while for the other ethyl alcohol or the neutral salt of lactic or pyruvic acid would serve equally well. Or he might make up a medium of neutral reaction containing phosphoric acid and certain inorganic salts, with a single amino acid like leucine or alanine as the sole organic material, and find that the grass bacillus grew readily on this, whereas the tubercle bacillus did not. In either case he would be dealing with a distinction in carbon metabolism.

If he attempted to distinguish them on the basis of nitrogen metabolism, he would be working on a more difficult problem, for he would find that, if hard enough pressed, either one could satisfy its nitrogen requirement with ammonia alone or with the nitrogen of simple amino acids or acid amides, as alanine or propionamide. He might be able to make some distinction on the readiness with which they abstracted that ammonia from different nitrogenous combinations, however, although he has little enough information to go on at present. For instance, in their action on amines, certain differences might be noted, inasmuch as some of the grass bacilli have been found to deaminize ethyl amine. The tubercle bacillus as well as a good many of the saprophytic acid fasts do not. Again, in their utilization of imino nitrogen, as seen in the compound creatinine, a more marked difference is shown, as this nitrogen seems unavailable for the tubercle bacillus, while a larger number of the saprophytes, including several strains of grass and smegma bacilli, in my experience, are able to grow on this compound as sole source of nitrogen, presumably hydrolyzing it and thus securing amino nitrogen. Also he might find that certain combinations of nitrogen and carbon,

while not necessary, were favorable. Indications have been found that the diamino acids and tryptophane favor growth, just as they do in animal life, perhaps because they are a necessary part of bacterial protein molecules, and their synthesis is a matter of some difficulty. That both organisms possess the capacity for synthesizing the aromatic rings, however, if forced to do so, may be readily proved by growing them with an ammonium salt as the sole source of nitrogen and testing the product some generations removed, for tryptophane, tyrosine and purine bases. The tests would be positive.

All in all, much is yet to be done to furnish an adequate basis for correlating metabolism and virulence. Some of the lines are so open, and so obviously important, that I feel like apologizing for coming before you tonight, as a worker in the field, to report that some of the most promising have been scarcely touched. For instance, to mention just one, much of natural resistance of the tubercle bacillus to digestion *intra vitam* has been attributed to its high wax content. But the avirulent acid-fasts have a high wax content too—at least the few of them so far examined. What is the difference? *

So far we have considered chiefly intake and synthesis in our brief reflection on the metabolism of the tubercle bacillus. The other side, catabolism and excretion, is at least as important from our point of view. As the tubercle bacillus grows in a bouillon culture, or in the disintegrated tissue of a caseous tubercle, diffusible molecules of the medium must be passing through its semi-permeable tissue all the time, there to meet certain enzymes which knock off various parts of the molecule, some of which are retained by the cell, caught on the fly so to speak, while others diffuse back into the medium. The chief blocks so chipped off are ammonia, various acids from the amino acids, and oxidation products of the carbohydrates. The variation in the amounts cast out leads to those more or less characteristic changes in reaction depicted in the Theobald Smith curve.

Now these simple substances are not the only materials getting out of the bacilli into the medium. For the medium of growth, freed from bacilli, now possesses certain properties not conferred by the products of metabolism just mentioned. It contains something which is poisonous to a tuberculous animal. Inasmuch as the symptoms elicited by this broth are the same as those called forth by any sort of watery extract of tubercle bacilli, carefully washed though they be from adhering broth, it may be assumed with some confidence that it is some product of the bacteria in the broth, and not the reverse, which causes the reaction. Now what of their own substance have the bacilli contributed to the surrounding medium in the weeks or months of their growth? A not unnatural supposition is that some have died and autolyzed, furnishing a certain amount of the products of protein autolysis. Somewhat against this hypothesis is the well known fact that tubercle bacilli do not autolyze to any great extent. Still a very little might be produced of a very potent substance.

That tuberculin is not a product formed extracellularly by action on the constituents of the medium, is practically certain, inasmuch as strong tuberculins can be made from simple media, like ammonium phosphate plus glycerol. In fact such media furnish the best material for a study of the nature of tuberculin, since there are no complex interfering substances. Now if tuberculin is protein in nature, like other materials concerned in immunity, it seems as if such media should be ideal for proving that fact. And yet just here there is the most amazing discrepancy of results. A half a dozen men, including Lockemann, report growing tubercle bacilli on such media, filtering them off cleanly, obtaining a true tuberculin with the material, and precipitating by ammonium sulphate or alcohol a substance in it which gave all the protein reactions, and was itself active as tuberculin. And a half a dozen other men, including Löwenstein and Pick, get no such thing. They get an active tuberculin, to be sure, but it gives no protein reactions. As far as my own experience goes, I have twice made tuberculins, once by growth on an ammonium chloride-glycerol medium, and once on an alanine-glycerol medium, which were active on tuberculous guinea-pigs, but gave no protein reactions, not even the simple biuret test.

In favor of the view that it is protein in nature, are the experiments of a number of investigators who have weakened or destroyed tuberculin by the action of such proteolytic ferments as pepsin, trypsin and erepsin. Perhaps, when the problem is solved, it will be found that tuberculin is a polypeptid, an autolytic product of the tubercle bacillus, protein in its nature in that it is derived from protein, but not sufficiently complicated in its structure to give the usual protein tests. This finding would force us to modify some of the prevailing concepts of immunity. Certainly an attractive problem here awaits solution.

One more word before I pass to the subject of the metabolism of the infected host. That concerns the conditions under which bacteria, even parasites, may multiply within a living body. The researches of Rettger and his associates have pretty definitely brought out the fact that bacteria are unable to grow on pure proteins or coagulated proteins, or in many instances even on pure proteoses or peptone. They need a certain amount of still simpler products of protein digestion from which to construct their enzymic machinery for the cleavage of larger molecules. This is a significant point in their

* It has been learned, since this address was given, that while the total quantity of lipin in tubercle bacilli and saprophytic acid-fast bacilli is about the same, the proportion of that lipin as wax is much higher in the tubercle bacillus.

relation to live cells. Living protoplasm contains no great amount of the simple molecules which are favorable to bacterial growth; consequently, living tissues are a poor feeding ground for germs. Once these tissues die, however, or, in other words, once the rate of catabolism greatly exceeds anabolism, or the latter ceases altogether, autolytic products accumulate, and the conditions for bacterial multiplication are at once established. This point will be referred to again when we come to consider the relation of the growth of the tubercle bacillus to necrosis. Doubtless many other important factors are concerned, such as the oxygen and carbon dioxide tensions, as has been so well brought out in the work of Wherry and Ervin and in the very interesting recent investigation by Corper. Death of the tissues probably plays a rôle here too.

So much for the present concerning bacterial metabolism.

A discussion of the other side of the picture, namely, the altered physiology of the host, properly begins with a consideration of the most characteristic lesion of tuberculosis, caseation. In this type of necrosis, tissue becomes pale grey or yellowish in color, with a certain resemblance to cheese, which is indeed closer from the point of view of chemical composition than that of appearance to the eye, the necrotic mass consisting, like cheese, essentially of coagulated protein and finely divided fat. The protein is chiefly simple protein, not nucleo—or otherwise conjugated. In fact the lessened amount of nuclear material, such as phosphoric acid and purine bases, is one of the striking chemical differences between caseous and normal tissues. Autolysis, which is on an extremely low plane, has at least gone far enough to bring these nuclear components into diffusible form. The total amount of protein is about the same as in the corresponding area of normal tissue, as is that of lipins, although certain qualitative differences are to be noted in each group. The proportions of cholesterol and lecithin are altered, and the iodine number, or index of nonsaturation of lipins, is changed, but the variations from normal are not so great as to cast doubt on the assumption that the caseous matter consists almost entirely of disintegrated pre existing tissue, modified to a slight extent by slight autolysis and the introduction of a small amount of foreign protein and lipin from the bodies of tubercle bacilli.

The cause of caseation necrosis in tuberculosis is still unsettled. Some investigators have claimed specific coagulating properties on the part of substances in the body of the tubercle bacillus. Auclair years ago reported producing caseation with a certain fraction of the fatty material. Morse makes a similar report today. Ruppel obtained a protamine, which he called "tuberculosamine," which like other protamines caused a precipitation of proteins from their solutions. Others have considered caseation as allied to the Arthus phenomenon, the result of the lodgment of a foreign protein on highly sensitized soil. In this case we are perhaps to think of cleavage of the foreign protein with the production of a toxic, coagulating fraction. It seems to me, however, that too much emphasis cannot be laid upon the unquestioned condition of local anemia as a causative factor in necrosis. The mechanism of its production offers room for argument, although several plausible explanations are readily thought of. The entering bacillus may produce substances causing an initially minute amount of capillary thrombosis, enough to produce necrotic material capable of giving sustenance to the bacilli present. However, the anemia may be more simply explained. Every entering mass of tubercle bacilli is promptly met by a perfectly non-specific foreign body reaction, the proliferation of a fixed phagocyte, the so-called epithelioid cell. The mere multiplication of these cells in a given area must be sufficient, through the pressure exerted, to shut off some of the capillary circulation, as Mallory explains necrosis in typhoid fever. Thus a local anemia may be readily established, with subsequent death of the cells of the anemic area. Then, and not until then, the conditions for bacterial multiplication are established, the bacilli obtaining the nutriment which they were unable to obtain from living cells from the autolytic products of the dead ones. After this start bacilli are transported, one way or another, to neighboring areas and an endless chain of foreign body reaction, anemic necrosis, and bacillary proliferation established.

A more difficult problem is to explain the long continued chemical *status quo* of the caseous tissue. In some way this must be dependent upon the presence of the tubercle bacillus. The like is not often seen in other forms of necrosis. An anemic infarct shrinks as its substance is slowly absorbed and replaced by entering fibroblasts. A cancerous nodule becomes umbilicated as its central anemic mass degenerates and diffuses away. But in the tubercle, the fibroblasts, although they may ring the lesion in leathery form, have little tendency to enter on radiating lines, while solution of the central, morphologically disintegrated tissue by autoenzymes is conspicuous by its absence. The lack of chemotaxis for motile cells is perhaps explained by the failure of the cellular enzymes to liberate diffusible products. Certainly extractives are present in but minute amount. Even in extreme cases of fluidity, as in cold abscesses, the crystalline products of the autodigestion of proteins are almost absent. Nor can proteases be demonstrated by the Müller-Jochmann plate method. Why this fundamental failure of autolysis? Have the autolytic enzymes been destroyed, or are they merely held in a state of inactivity? Jobling and Peterson have furnished some interesting information on this point. They noted first, that proteolytic action in general, and autolysis in particular, were inhib-

ited by the soaps of unsaturated fatty acids, while not affected by the saturated ones; secondly, that caseous areas, which characteristically did not autolyze rapidly, contained such soaps in appreciable amount; and thirdly, that the saturation of these soaps with iodine removed their antiproteolytic action, following which autolysis pursued a normal course. Finally, they were able to demonstrate the presence in the tubercle bacillus itself of unsaturated fatty acids, the soaps of which are more active in proportion to their iodine value in inhibiting trypsin and leucoprotease than soaps of linseed and olive oil, and that these soaps too can be deprived of their inhibitory action by iodine. Their conclusion naturally was that the unsaturated fatty acids of the tubercle bacillus are a very important factor in the failure of absorption of caseous tissue. I have always felt that this piece of work is very much in need of amplification. For instance, it would be desirable to know if the leprosy bacillus, which excites a foreign body reaction without caseation, is devoid of these antiproteolytic properties.

We may next consider this caseous mass for its bearing upon the physiology and metabolism of the host. It has its specific and non-specific elements, as far as tuberculosis is concerned. In the first place, it contains tubercle bacilli, which, chemically considered, are foreign proteins, proteins which by their continued presence within the body have so sensitized the tissues of that body that they react, more or less violently with hyperemia and exudation, to the same material, whether it arrive at a given point by dissemination from the original focus, or by fresh introduction from without. Yet it is unlikely that this reaction to "tuberculin" accounts for all, or even the greater part of the toxemia of tuberculosis. For, secondly, the tissue of the caseated area, once homologous, before its coagulation, has now become a foreign protein too. Whether the body is allergic toward it, as it is to tuberculo-protein, is a question. Be that as it may, the substance is appreciably toxic *per se*. The toxicity of the products of incomplete protein digestion, proteoses and peptones, is too well known to require comment. But is much of such diffusible substance present in the caseous tubercle? We have noted before that self-digestion of the caseous mass occurs on but a small scale.

In this connection may we not refer to a very instructive set of experiments by Dr. Krause? You are doubtless quite familiar with these; yet they seem to me so important for our conception of the chemistry of the disease that I cannot refrain from repeating their story in some detail. Krause started out with the idea that foci at the height of reaction probably contained more toxic material than non-reacting foci. Accordingly, to prove this he gave large doses of tuberculin to tuberculous guinea-pigs, killed them off during the acute stage of the subsequent illness, and found, as he knew he would, that the tuberculous foci were in a condition of inflammatory reaction. He then emulsified these inflamed foci in physiological saline, centrifuging the product to remove masses of a size sufficient to act as emboli, and injected the clear juice intravenously into normal animals. He found, as he anticipated, that the material was highly poisonous. Then he went a step further. He injected emulsions similarly prepared from the non-reacting foci of animals which had never received tuberculin. Somewhat to his surprise, I believe, he found that such emulsions too were markedly toxic, as much so as the first ones. He next took tissue from healthy guinea-pigs, emulsifying and injecting normal organs, and found that this material too was toxic for normal animals, and furthermore, just as much so as that from a tuberculous focus. If any of these emulsions were filtered, however, through a Berkefeld candle, the product was no longer toxic. These experiments indicated to Dr. Krause that an animal is poisoned by any kind of cellular material which gets into its blood stream in large amount in unit time. An abundance of confirmation of these experiments on the effects of tissue juice in the blood stream of normal animals has accumulated in the literature of fields other than tuberculosis. The recent experiments of Karsner and Hanzlik and of Mills are instructive. It is especially interesting that lung tissue furnishes exceptionally toxic substances. All these investigations prove, I believe, that a storehouse of disintegrating protein, even though inhibited in its autolysis to such an extent that no great amounts of toxic proteose and peptone are absorbed, is yet a source of poison to the organism containing it. On the periphery of each caseous mass in the body of a consumptive a certain amount of this material must be all the time being swept into the circulation. Any condition which will increase the circulation at that point naturally will favor absorption. Such a condition occurs in the focal active hyperemia which follows the administration of tuberculin, or the dissemination of tubercle bacilli to fresh but sensitized soil, the latter being a process constantly occurring in progressive tuberculosis. Thus, the toxemia of progressive tuberculosis may be thought of as to a considerable extent non-specific in character, dependent upon the absorption of disintegrating protein, but it must be continually borne in mind that it is aided, in the manner noted, by one which is quite specific in nature, the focal inflammatory reaction to tuberculo-protein.

Let us now take up the alterations in the physiology of the host, dependent upon absorption from his focus, regardless of the site of the latter, so long as it is in a sufficiently unprotected state, leaving out of consideration those changes in metabolism which depend upon the location of the lesion, such as the diminished gas exchange following obliteration of lung volume, or dis-

turbed absorption resulting from intestinal ulceration, which also have sequelæ of abundant chemical interest.

One of the most striking clinical manifestations of this absorption is fever. And in a perfectly non-specific manner to a certain extent changes are produced in the patient's metabolism, not because he has tuberculosis, but because he has fever. This is hardly the place for a discussion as to the cause of the fever in tuberculosis, but we may simply recall the fact that, since the time of Traube, fever has been attributed to a diminution in the ability to discharge the heat produced, the regulatory control being lost through the action of some poison upon the vasomotor centers, and we may state further that according to modern opinion, developed largely from the work of Vaughan, that poison is frequently protein in nature. Indeed there is much ground for believing that the fever in tuberculosis is, like the fatality in the case of Dr. Krause's guinea-pigs, due to the presence, in the blood stream, of foreign protein or protein cleavage products, and that these in turn have two sources, tuberculoprotein and the protein of the disintegrating caseous mass, of which two the latter is by far in excess.

Whatever be the mechanism involved in the production of fever, once fever is established, metabolism may be modified more or less profoundly as a result of it. "Warmed tissue metabolizes more material than cooled tissue," writes Lusk, citing the classic experiments of Pflüger, who curarized rabbits, thus paralyzing their voluntary muscles and capacity for increased work, at the same time applying external heat, and noted that as the rectal temperature rose from 39° to 41° the oxygen absorption increased 10 per cent for each degree. Plenty of confirmation has appeared since the time of Pflüger, and a large literature has accumulated on the nature of the material metabolized. That basal metabolism is increased in tuberculosis has recently been shown by Grafe, who found in twenty patients a raising of heat production per kilogram varying between 10 and 80 per cent, the higher figures being for febrile cases. Whether such metabolism can be considered "basal" is a technical question discussed by McCann and Barr, who also note an increased metabolism in fever, which at 40° may be 30 per cent above normal.

The effect of fever upon protein metabolism and nitrogen elimination is more complicated. One of the most interesting investigations on the subject was that of F. Voit, who found that artificially raising the temperature of a fasting dog to 40-41° for twelve hours increased the nitrogen elimination 37 per cent above normal. That the action was not a selective one upon protein, however, was indicated by the fact that a preliminary feeding of 30-40 grams of sugar prevented this increase in protein metabolism, which was thus seen to be simply a part of the general increase, occurring only when the store of more readily burnable glycogen was depleted. That a loss of nitrogen occurs in infectious fevers has long been known, and that this is greatest during the height of fever is also generally true.

How much of it, however, is due to the fever and how much to more direct action of the absorbed material which causes the fever, remains to be determined. Many writers speak of a toxic destruction of protein. May, for instance, says, in the conclusion of his comprehensive review of the subject of metabolism in tuberculosis: "The wasting of tuberculous subjects is due primarily to poisons absorbed from tuberculous nodules. Large doses cause a direct injury to cell protoplasm. The amount of protein destruction attributable to this cause is not very large, but becomes of importance when continued for a long period of time and when there is no compensatory regeneration. It appears that the power to regenerate on the part of these cells injured by toxins is greatly reduced and in severe cases entirely lost." He goes on to write, however, "Higher degrees of toxic action are usually accompanied by fever, and the metabolism of the febrile consumptive follows the same laws as metabolism in the fever of other causes. There is an increased protein destruction, but not an increased fat metabolism, except as may incidentally result from dyspnea, chill or muscular activity."

Graham and Poulton, in Friedrich Müller's clinic, have showed that in man a body temperature of 40.2°, brought about through the influence of a steam bath, does not of itself cause an increase in the metabolism of protein. In their carefully controlled experiments the abnormally high body temperature was maintained for several hours and yet there was never any increase in the breakdown of body protein as the result of hyperthermia. Coleman and Dubois, in their investigation on the metabolism in typhoid fever, found it impossible to escape the conclusion that the destruction of protein was caused by the toxins of the disease, noting that in some cases protein destruction continued for several days after body temperature had reached a low level. In their recent work on tuberculosis McCann and Barr adopt a similar point of view concerning the cause of protein destruction, and find that in this disease the toxic destruction is conspicuously less than in typhoid fever. An interesting finding in tuberculous patients was normality in the specific dynamic action of proteins, indicating that ingested protein was undergoing normal catabolism, and not serving merely as partial replacement of greatly wasted tissue proteins, as seemed to be the case in Coleman and Dubois' typhoid patients, who, probably because of the high level at which protein metabolism was being maintained, failed to show the normal specific dynamic action of ingested protein. That some toxic destruction occurred, however, was shown by their results on the minimum nitrogen excretion of the tuberculous organism, 5-6 grams per day, somewhat more than that which

may be obtained in healthy men, although distinctly less than the lowest obtainable in typhoid fever. I may add that Ahlquist has found that while normal children, four to nine years of age, showed a retention of at least 20 per cent of the nitrogen absorbed, tuberculous children of the same age retained only 8-14 per cent. This is confirmatory experimental evidence for an impression we have long held concerning the growing tuberculous child.

Summarizing the results of the investigations cited we may conclude that in progressive tuberculosis the rate of metabolism is increased, as a result of the operation of two factors, hyperthermia and the toxic effect of a foreign protein upon protoplasm. As far as protein destruction is concerned, the second of these seems to be the more important, for hyperthermia *per se* does not increase nitrogen elimination in the normal subject. Yet it may well be that in the increased general metabolism induced directly by fever, the tissues become impoverished in those protein-sparing constituents which serve to prevent protein destruction at similar temperatures in health, and that protein may for this reason be drawn upon to maintain the high level of total energy transformation.

In less severe, afebrile tuberculosis such tissue destruction as does take place is probably the result of the action of some poison upon the cells. McCann and Barr's results justify the conclusion that in such cases basal metabolism is but little altered, and protein metabolism but slightly above the normal. Even Grafe, who noted an increase in basal metabolism which at times reached 80 per cent, comments on the marked conservation of the afebrile tuberculous organism for its protein nitrogen.

Going back to reconstruct our chain of chemical factors involved in the progression of tuberculosis we have the tubercle bacillus as the first link, a wax-armored microörganism, maintaining itself in necrotic tissue, picking and choosing its nutriment from the heterogeneous mass set before it, utilizing the glycerol of hydrolyzed fats, and probably building its wax therefrom, taking ammonia from certain of the amino acids produced in the digestion of dead protein, utilizing others directly to speed up the process of synthesis of its own protein, autolyzing to a slight extent, sufficiently to sensitize the surrounding host to its diffusible protein products, being carried by the lymph, by phagocytes or otherwise, to new soil, there to be met by a non-specific foreign body response, which in the end operates to produce anemia and death of the isolated cells. Then we have the failure of that dead tissue to autolyze, perhaps because of the presence of ferment-inhibiting substances within the bacillus, the phenomenon of caseation. Finally, there is more or less absorption of foreign protein from that focus, that of the bacillus itself and that of the disintegrating tissue, both toxic to the body protoplasm, both capable of causing fever and stimulating the metabolism of the host, so that in severe cases the typical picture of consumption ensues. I feel that this is a very sketchy treatment of a tremendous subject, and that some of the conclusions drawn may prove incorrect, but they may serve to draw attention to the intricate chemical mechanisms involved in the disease.

# THE DISSEMINATION OF BACTERIA IN THE UPPER AIR PASSAGES

## III. THE RELATION OF BACTERIA TO THE MUCOUS MEMBRANES

By Arthur L. Bloomfield

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In the preceding papers of this series [1] it was shown that bacteria and foreign particles introduced into the mouth are carried back by definite currents and rapidly eliminated. In certain cases, to be sure, foreign organisms may persist for long periods of time, but in such instances they are usually found in a focus of diseased tissue such as an infected tonsil. The free mucous surfaces of the mouth and tongue, on the other hand, preserve a fairly simple and constant flora and foreign organisms deposited thereon are usually rapidly eliminated. The question, therefore, arises as to what prevents the removal and elimination of the "normal" flora. Why does the tongue not rid itself of its habitual flora just as it does of foreign organisms? It has usually been assumed that the harmless "mouth bacteria" were growing freely in the buccal secretions just as they might in a test-tube of broth. But the above considerations would seem to indicate that some firmer union must exist between the microorganisms and the mucous membranes of the host. The present communication deals with the nature of this union and its mechanism.

### Methods

The general method of approach was based on the following considerations. If the members of the habitual "normal" flora of a healthy mucous membrane are merely growing freely on that surface in the mucous layer, it should be possible by some process of intensive cleansing to remove a large part or all of such organisms. If bacteria still persist in spite of such procedures, one must assume a very close affinity, both functional and anatomic, between the organisms and the mucous mem-

brane, quite analogous to that which obtains in the case of a foreign pathogen and a focus of diseased tissue.

In the first group of experiments attempts were made to remove the bacterial flora of the tongue by washing with water. The individuals studied were all healthy men with clinically normal buccal cavities. The tongue was the point of attack because it lent itself most readily to the experimental procedure.

EXP. I. Dec. 8, 1921. The mouth was thoroughly rinsed with water and the anterior half of the tongue was then alternately flushed and scrubbed with sterile gauze pledgets for five minutes. Cultures were made before and after the procedure from approximately the same spot on the tongue and they were plated by similar methods on various media. Results of Cultures: (aërobic methods only).

| *Culture before washing* | *Culture after washing* |
|---|---|
| (1) ∞ Gram-negative cocci | (1) ∞ Gram-negative cocci |
| (2) Many M. Tetragenus | (2) Many M. Tetragenus |
| (3) ∞ non-hemolytic streptococci | (3) ∞ non-hemolytic streptococci |
| (4) Many hemolytic influenza bacilli | (4) Many hemolytic influenza bacilli |

*Comment:* The cultures showed no qualitative or quantitative change in the flora after the above procedure.

EXP. II. Jan. 3, 1922. The same procedure was employed, but the washing was kept up for fifteen minutes.

| *Culture before washing* | *Culture after washing* |
|---|---|
| (1) ∞ M. Tetragenus | (1) ∞ M. Tetragenus |
| (2) A few Gram-negative cocci | (2) A few Gram-negative cocci |
| (3) Many grey streptococci | (3) Many grey streptococci |
| (4) Many green streptococci | (4) Many green streptococci |
| (5) A few pin-point alpha hemolytic colonies (not identified) | (5) A few pin-point alpha hemolytic colonies (not identified) |

*Comment:* After washing the tongue with water for fifteen minutes there was no qualitative change in the flora. In this experiment there seemed to be a slight quantitative decrease in the number of colonies but it was within the limit of error of swab-culture technique.

EXP. III. Jan. 5, 1922. In this experiment it was decided to push the effect of washing with water to the limit. Three procedures were carried out successively. First the mouth was thoroughly rinsed, then the anterior part of the tongue was scraped with the teeth and finally it was scrubbed with sterile gauze. These three manœuvers were repeated continuously for thirty minutes. At the end of this time the tongue was irrigated with five liters of water. Cultures were made from the same spot on the anterior tongue before the experiment, after the thirty minute period of washing, after thirty-five minutes, and after sixty minutes.

| *Culture before washing* | *After 30 minutes* | *After 35 minutes* | *After 60 minutes* |
|---|---|---|---|
| (1) ∞ M. Tetragenus | (1) ∞ M. Tetragenus | (1) ∞ M. Tetragenus | (1) ∞ M. Tetragenus |
| (2) ∞ Gram-negative cocci | (2) ∞ Gram-negative cocci | (2) ∞ Gram-negative cocci | (2) ∞ Gram-negative cocci |
| (3) Many green streptococci | (3) Many green streptococci | (3) Many green streptococci | (3) Many green streptococci |
| (4) Many grey streptococci | (4) Many grey streptococci | (4) Many grey streptococci | (4) Many grey streptococci |
| (5) A few hemolytic influenza bacilli | (5) A few hemolytic influenza bacilli | (5) A few hemolytic influenza bacilli | (5) A few hemolytic influenza bacilli |
| (6) A few Staph. aureus | | (6) A few Staph. aureus | (6) A few Staph. aureus |

*Comment:* After washing for *thirty* minutes there was no qualitative or quantitative change in the cultures save that Staph. aureus which was present in very small numbers in the control was absent. Inasmuch as it was recovered in the two following controls, this absence in one culture must be an experimental error which is to be expected with the crude swab method where only a few organisms are present.

EXP. IV. Jan. 10, 1922. The mouth was thoroughly rinsed with water and the tongue was then scrubbed with water and a stiff toothbrush with frequent irrigations. At the end of fifteen minutes the scrubbing had progressed to a point where the tongue began to bleed, and the experiment was discontinued. Cultures were made before and after the scrubbing from the same site.

| *Culture before scrubbing* | *Culture after scrubbing* |
|---|---|
| (1) Many M. Tetragenus | (1) Many M. Tetragenus |
| (2) A few hemolytic influenza bacilli | (2) A few hemolytic influenza bacilli |
| (3) Many Gram-negative cocci | (3) Many Gram-negative cocci |
| (4) Many green streptococci | (4) Many green streptococci |
| (5) Many grey streptococci | (5) Many grey streptococci |
| (6) A few Gram-positive diphtheroids | (6) A few Gram-positive diphtheroids |

*Comment:* There was no demonstrable qualitative or quantitative change in the flora after the above procedure.

### DISCUSSION OF EXPERIMENTS I-IV.

It will be seen from the control cultures that the organisms present on the tongue at the start of the experiments were members of the "normal flora"—that is to say, organisms which are present in practically all healthy mouths and which are found widely spread throughout the mucous membranes of tongue, cheeks, tonsils and pharynx—with the exception of the hemolytic influenza bacillus, and the staph. aureus in Experiment III. While some of the bacteria were undoubtedly removed in the washing process, the number was relatively so small that there was no demonstrable change in the appearance of cultures made after the most vigorous sort of a scrubbing process. It becomes clear, then, that the members of the "normal habitual" mouth flora are not simply growing free in the mouth secretions but that they are intimately bound to the mucous membrane just as are foreign organisms in a focus of infection. Their complete removal is apparently no more readily effected than that of diphtheria bacilli, for example, which are breeding in the depths of an infected tonsil. The nature of this adhesion to the mucous membrane will be discussed below, but further attempts at removal by other means will first be described.

The preceding experiments had indicated that the actual breeding place of the mouth flora must be beneath

the layer of mucus and very near to the actual cells of the mucous membranes. Means of drawing the organisms out and making them more accessible to the washing effect of irrigations were considered. It seemed possible that strongly hypertonic solutions might produce the desired result. Sodium chloride was therefore tried.

Exp. V. December 13, 1921. The mouth was washed and the tongue was then scrubbed with saturated salt solution for ten minutes. At the end of this time it was irrigated with two liters of water.

| *Culture before procedure* | *Culture after procedure* |
|---|---|
| (1) ∞ M. Tetragenus | (1) ∞ M. Tetragenus |
| (2) Many Gram-negative cocci | (2) Many Gram-negative cocci |
| (3) Many non-hemolytic streptococci | (3) Many non-hemolytic streptococci |
| (4) Many hemolytic influenza bacilli | (4) Many hemolytic influenza bacilli |

*Comment:* No demonstrable qualitative or quantitative change in flora.

Exp. VI. A piece of rubber dam with a window about 3 cm. square was placed on the tongue. This allowed manipulations without contamination of the experimental area by the saliva. A paste of sodium chloride was applied to the tongue. The subject almost immediately experienced a strong burning sensation. After three minutes the salt was washed off and the tongue thoroughly irrigated with water. The salt pack was then reapplied and the above procedures repeated for fifteen minutes. Cultures were made before and at the end of the experiment.

| *Culture before salt application* | *Culture after salt application* |
|---|---|
| (1) ∞ M. Tetragenus | (1) ∞ M. Tetragenus |
| (2) Many Gram-negative cocci | (2) Many Gram-negative cocci |
| (3) A few hemolytic influenza bacilli | (3) A few hemolytic influenza bacilli |
| (4) A few green streptococci | (4) A few green streptococci |
| (5) A few grey streptococci | (5) A few grey streptococci |
| (6) 1 colony Staph. albus | |

*Comment:* No quantitative or qualitative change made out.

Exp. VII. The tongue was scrubbed and irrigated with a saturated solution of sodium bicarbonate for five minutes.

| *Culture before bicarbonate* | *Culture after bicarbonate* |
|---|---|
| (1) ∞ M. Tetragenus | (1) ∞ M. Tetragenus |
| (2) Many Gram-negative cocci | (2) Many Gram-negative cocci |
| (3) ∞ non-hemolytic streptococci | (3) ∞ non-hemolytic streptococci |
| (4) A few Gram-positive diphtheroids | (4) A few Gram-positive diphtheroids |

*Comment:* No qualitative or quantitative change made out.

Exp. VIII. Similar to Experiment VI, except that a pack of bicarbonate of soda was applied for fifteen minutes.

| *Culture before procedure* | *Culture after procedure* |
|---|---|
| (1) ∞ M. Tetragenus | (1) ∞ Tetragenus |
| (2) Many Gram-negative cocci | (2) Many Gram-negative cocci |
| (3) A few hemolytic influenza bacilli | (3) A few hemolytic influenza bacilli |
| (4) A few green streptococci | (4) A few green streptococci |
| (5) A few grey streptococci | (5) A few grey streptococci |

*Comment:* No qualitative or quantitative change made out.

Exp. IX. It was thought that possibly the adhesive qualities of mucus might have prevented to some extent the removal of organisms by the foregoing procedures. Sodium carbonate which is a solvent for mucus was therefore tried. The tongue was scrubbed and irrigated for fifteen minutes with two per cent sodium carbonate—the greatest concentration that could be endured.

| *Culture before procedure* | *Culture after procedure* |
|---|---|
| (1) ∞ M. Tetragenus | (1) ∞ M. Tetragenus |
| (2) Many Gram-negative cocci | (2) Many Gram-negative cocci |
| (3) A few green streptococci | (3) A few green streptococci |
| (4) A few grey streptococci | (4) A few grey streptococci |

*Comment:* No demonstrable qualitative or quantitative change.

## Summary

In summary then it appears that it was found impossible to alter the character of the flora of the tongue as revealed by aërobic surface cultures by any of the above procedures. Many organisms were undoubtedly removed, but the experiments show clearly that the normal mucous membranes of the tongue can not be washed free of bacteria. It seems fair to conclude, therefore, that the organisms which are found in the normal mouth so uniformly as to constitute in a sense a normal flora are not growing free in the secretions but are in actual and vital contact with the mucous membrane.

A study of stained sections of the tongue shows a mucous membrane not unlike the skin in structure. The covering layer of stratified squamous epithelium is thrown up into microscopic folds and the actual living surface is more or less covered by desquamated shrunken cells which again suggest a cutaneous keratosis. Furthermore, the mucous membrane is everywhere perforated by the orifices of the minute mucous glands. We believe that the actual niduses of growth of the bacterial flora is in these crevices in the epithelium and in the gland orifices. Here there is a localization of the bacteria. As they multiply, certain organisms are thrown off and are removed just as are foreign particles or bacteria experimentally introduced. Hence we have a constant stream passing out from a source which is relatively fixed and therefore allows the persistence of a bacterial species on the normal mucous membranes of the mouth for indefinite periods of time.

If the above conclusions are correct, it seemed probable that a foreign organism placed on the tongue could be readily washed away, inasmuch as there was no actual growth in the superficial layers of the mucous membranes. The next experiments were aimed at settling this point.

Exp. X. The entire twenty-four growth from an agar slant of Sarcina lutea was smeared on the anterior part of the tongue. A culture was immediately made. The tongue was then vigorously scrubbed with water for five minutes and another culture was made.

| *Culture immediately after application of Sarcina* | *Culture after washing for five minutes* |
|---|---|
| (1) Innumerable colonies of Sarcina — plate covered with a confluent yellow growth. | (1) 2000 colonies Sarcina lutea.<br>(2) The usual tongue flora in normal proportions. |

*Comment:* In contrast to the preceding experiments it was possible in five minutes to wash away the vast majority of the artificially implanted organisms.

EXP. XI. A similar experiment was performed, a twenty-four hour agar slant of Staphylococcus albus being employed.

| *Control culture* | *Culture immediately after applying albus* |
|---|---|
| Usual tongue flora (no Albus) | Innumerable colonies of albus —confluent growth |
| *After washing for 5 minutes* | *After washing for 10 minutes* |
| About 200 colonies albus + usual mouth flora | About 100 colonies albus + usual mouth flora |

*Comment:* Washing for five minutes removed almost all of the Staphylococci introduced, although even after ten minutes a few colonies still were present.

### DISCUSSION OF EXPERIMENTS X AND XI.

It is seen that even ten minutes vigorous washing did not serve to remove all the colonies of a foreign organism experimentally applied. The reduction being so vast and striking, however, in contrast to the response of the indigenous organisms under similar treatment, it may fairly be concluded that an essential difference exists in the relation to the mucous membrane of an organism adapted to growth in the mouth and a foreign organism experimentally introduced. The latter behaves like an inanimate foreign particle.

The next point to be tested was the following. If the actual growing and multiplying fraction of a mouth inhabitant such as Streptococcus viridans is located in the mucous membrane and if there is a balance of power at this point among the various members of the flora which regulates their relative proportions, the reintroduction of an autogenous strain in large quantity should be followed by a rapid disposal of the organisms introduced just as is the case with foreign bacteria. This question was approached as follows.

A culture was made from the tongue of Individual B. The predominating strains of green streptococcus and of M. tetragenus were isolated.

EXP. XII. A culture was made from the tongue and immediately thereafter the twenty-four hour growth from a blood-agar plate of the autogenous strain of S. viridans was placed on the tongue. Cultures were made immediately after application and two hours later.

| *Control culture before inoculation* | *Culture immediately after inoculation with S. viridans* |
|---|---|
| Usual tongue flora | Plate almost pure S. viridans |
| *Culture two hours later* | |
| Same organisms as in control and in about same proportions. | |

*Comment:* The autogenous strain of Streptococcus, when re-introduced, did not colonize, but was eliminated just as were foreign organisms.

EXP. XIII. Procedure similar to that of Exp. XII, an autogenous strain of M. tetragenus being employed.

| *Control* | *Culture immediately after inoculation with M. tetragenus* |
|---|---|
| Usual tongue flora | Plate almost pure Tetragenus |
| *Control two hours later* | |
| Same organisms as in control and in about same proportions | |

*Comment:* Result similar to that in Experiment XII.

### DISCUSSION OF EXPERIMENTS XII AND XIII.

In previous studies in which foreign organisms (B. coli, Staph. albus, B. influenzæ, B. Friedländer) were experimentally applied to the tongue, it was found that such organisms were rapidly eliminated, usually within a few hours.[2] From the present experiments it appears that a culture of an autogenous strain, when reintroduced, is eliminated just as is a foreign organism. It may be that even a single subculture on artificial media alters the bacteria in such a way that its adaptation is lost, but it seems more likely that as soon as the organism is withdrawn from its actual nidus of growth it is no longer able to reattach itself but is doomed to elimination. Be this as it may, we wish to use this experiment merely to emphasize further the point that the persistence of any organism on the buccal mucous membranes implies a close anatomico-biological reaction at the site of growth.

The facts brought out so far deal mainly with the so-called "normal" flora of the mouth—namely, groups of organisms so constantly and persistently present in healthy people that one must assume a high degree of general adaptation between the race of organisms as a whole and the population at large.

There exist, however, other groups of bacteria which are present much less frequently, and yet are often encountered in the normal mouth. Pneumococci, for example, are found in from thirty to fifty per cent of the general population, influenza bacilli in from twenty to thirty per cent, and hemolytic influenza bacilli in from thirty to fifty per cent. Now, although these organisms as a whole are clearly less highly adapted to growth on human mucous membranes than those considered above, the question remains open as to whether in the individual harboring them a different type of adaptation exists. More specifically stated, can the influenza bacillus or the pneumococcus, when growing in the mouth of a healthy person, be more easily removed than the members of the "normal" flora?

This point was a rather difficult one for systematic experimental approach, but certain suggestive observations were obtained. It was found that individual B was carrying hemolytic influenza bacilli on the tongue. Various attempts were made to remove this organism as follows:

December 8—Tongue scrubbed with water five minutes.
December 12—Tongue scrubbed with saturated salt solution five minutes.

December 13—Tongue scrubbed with saturated salt solution fifteen minutes.

December 16—Tongue scrubbed with saturated sodium bicarbonate for fifteen minutes.

Cultures made before and after the above procedures showed hemolytic influenza bacilli in similar numbers. On January 3, however, these organisms disappeared spontaneously, nor were they recovered thereafter.

This observation is in accord with the assumption which seems inevitable to us that any organism which persists on a normal mucous membrane for more than a few hours is in vital biological relationship to the mucous surface. Were this not so, it would be removed as a foreign particle by the normal eliminative mechanism. The bearing of this principle on the significance of the "carrier" in the spread of respiratory disease will be discussed at another time.

## Summary

The above experiments clarify some of the puzzles of mouth bacteriology. They explain, in the first place, why the organisms which have been regarded as members of the "normal" flora are able to persist and are not eliminated as are foreign bacteria experimentally introduced. They persist because their nidus of growth is actually in the mucous membrane—the organisms which are discharged from these niduses are already doomed to be removed. The situation is crudely analogous to that of the blood cells which are swept away from the parent cell-nests in the bone marrow. Indirectly, we also get the explanation for the fact, which at first seemed remarkable, that foreign organisms experimentally introduced into the mouth are so completely and rapidly eliminated, for it becomes apparent that to persist such organisms need more than a favorable salivary medium—an actual adaptive reaction with the mucous membrane, which is doubtless a biological process of the highest complexity and subtlety, must take place. The question of the importance of the saliva in the growth of organisms in the mouth is also clarified. The saliva, as a rule, plays no significant part either favorable or inhibitory. It now becomes intelligible why bacteria, such as colon bacilli, which thrive in saliva *in vitro*, are not found in the normal mouth, whereas organisms such as pneumococci or influenza bacilli, which die in saliva *in vitro*, are frequently present. The colon bacillus, despite its growth in saliva, is unable to react with the mucous membrane so that colonization there can take place; pneumococci, on the other hand, are able to do so, and their actual growth processes probably occur in the mucous membranes largely or entirely independently of overlying secretions. It is readily apparent why an organism located in a focus of infection does not spread from such a focus over the entire mouth and throat, and it is clear why an excess of an autogenous strain when reintroduced is promptly eliminated. No sooner has the organism been discharged from its nidus of growth than it is already altered to such a degree that return to colonization is unlikely. It becomes clear, then, that these biological adaptations are most delicate and sensitive, and further analysis may throw light on the essential mechanism of infection and of the production of the carrier state.

Furthermore, it becomes apparent that to speak of a "normal" flora is only appropriate in a broad clinical sense, indicating groups of organisms widely and constantly disseminated and usually harmless. From the biological point of view any organism which has established actual growth on a normal mucous membrane is, for the time being at least, just as normal an inhabitant as any other bacterium similarly adapted.

## Conclusions

1. No bacteria of any sort entering the mouth can persist free in the secretions for more than a few hours.

2. More permanent presence implies a biological adjustment to growth on the mucous membrane whereby the organisms become localized at the site of growth.

3. Such adaptive power is relatively constant for large groups of bacteria in relation to the general population, but varies widely in the case of individual organism and individual host.

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# THE CHANGES IN THE OMENTUM OF THE RABBIT DURING MILD IRRITATIONS; WITH ESPECIAL RFERENCE TO THE SPECIFICITY OF THE MESOTHELIUM

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The ease with which cells can be observed in the omentum, without the necessity of subjecting them to much manipulation, has caused this structure to be widely utilized in studying special characteristics of individual types of cells and their interrelationships, under both normal and experimental conditions. In a general way the histological investigations which have been conducted on the omentum can be divided into two groups. The investigations in one of these groups have been concerned with the genetic classification of the cells which constitute the tâches laiteuses, particularly with regard to their hæmatological relationships. The other group includes numerous studies which have been made on the characteristics and relationships obtaining between the three great groups of cells which constitute the general framework of the organ—the clasmatocytes, the fibroblasts, and the serosal lining cells. The serosal lining cells have received particular attention in this regard and much work has been done on their reaction to irritants and on the rôle played by them during the formation of adhesions.

The study of the lining cells covering the omentum has three salient features: the relation of these cells to the production of the free cells which are found in the exudate of the peritoneal cavity during inflammations, the relation of the serosal cells to the clasmatocytes, and finally, the relation of these lining cells to the fibroblasts which constitute the greater part of the framework of the organ. The first two questions are closely related and have been discussed elsewhere;[9] and the conclusion was reached that the majority of the free cells of the exudate were derived from the clasmatocytes, which, in the omentum, occur chiefly in the neighborhood of the blood-vessels and in the tâches laiteuses, though they are also to be found scattered through the entire omental network. The serosal lining cells were found to have no part in the formation of the true phagocytic mononuclears of the exudate, and no genetic relationship with the clasmatocytes.

In regard to the relationship of the lining cell to the fibroblast there has been much diversity of opinion; many of those who have studied the omentum during inflammatory reactions have concluded that these cells are capable of definite interchange in morphological and functional characteristics. Others have described similar appearances in the omentum but have left unsettled the question of the interchangeability of fibroblasts and serosal cells. And finally, a few have maintained the specificity of the serosal cells and the fibroblasts in the general serous membranes, but without any direct consideration of the omentum itself.

Ranvier[20, 21] was the first author to discuss the relation of the lining cells of the omentum to the other cells constituting the framework of that organ. His views have been widely accepted, and his conclusions supported by the observations of many workers; Cornil,[8] Marchand,[18, 19] Roloff[24, 25] Borst,[1] and others. Ranvier describes the omental lining cells as changing during a mild inflammation from characteristically outlined pavement cells to star-formed cells with long processes which he considers as wholly indistinguishable from the fibroblasts, and he concludes from such observations that these two types of cells are identical, at least so far as their reactions to irritation are concerned, and hence must be capable of easy interchange.

Among the more modern workers on this subject are Weidenreich[30] and Schott;[26] these observers, after long and minute study of the reactions of the peritoneal membranes, conclude that the lining cells of the omentum cannot be distinguished from the fibroblasts and that the two types of cells are entirely interchangeable. Schott, in his study on the cells of the serous cavities, derives the free cells of the peritoneal exudate from the serosal lining cells and the fibroblasts indiscriminately.

Kiyono,[15] on the other hand, after study of omental spreads and sections from animals vitally stained with carmine and trypan blue, states that he could never find any indication of a transition from lining cells to fibroblasts. He says that normally the lining cells form a continuous, characteristic cell-series over the entire omental surfaces, and that they can easily be differentiated from the fibroblasts. But he states that during inflammation a portion of the lining cells assume a form which greatly resembles that of the fibroblasts, and he therefore admits the possibility of a close relationship between the two. He is unable to state with certainty if the lining cells do, or do not, participate in the formation of new connective tissue.

Marchand's[18] description of the omentum in fresh preparations is very exact and deserves considerable

attention and credit. He studies the omentum after the introduction of a suspension of lycopodium spores, and describes the mesothelial cells, seven hours after the injection, as rounding up and their cytoplasm becoming finely vacuolated; these cells stand out clearly from the surface of the omental network. Twenty-four hours after the injection he found many delicate protoplasmic structures of various forms: flat, irregular masses of protoplasm with numerous processes which appeared and disappeared and long spindle-formed cells with finely vacuolated protoplasm. He states that the origin and relationship of these large, variously formed elements could not be determined in fresh preparations. From stained sections and preparations from later stages he concludes that all of the lining cells proliferate to form fibrillary structures, and later a part of these form fibrils and new connective tissue, the other part forming more lining cells. The former are the star-formed irregular cells, to which he assigns amœboid capabilities and which he believes, participate with the clasmatocytes in the formation of giant cells, while the latter become again the usual flat mesothelial elements.

Büttner [5] introduced cultures of staphylococcus aureus or weak silver solutions into the peritoneal cavity of guinea-pigs to produce inflammations. He studied the omentum carefully at varying intervals following this procedure and says, because of the complicated structure of the omentum, it is difficult, after irritation, to differentiate between the types of cells or decide which groups are undergoing mitosis. Although he leaves open the question of a possible transformation of lining cells into fibroblasts, he thinks his experiments show that the omentum is covered by a single layer of cells which react during inflammations as true epithelium. This was particularly well demonstrated in his sections cut perpendicularly to the surface where the differences between the cells on the surface and those constituting the subserosal tissue are very striking. In sections taken three days after the commencement of the inflammation he found areas showing evidences of regeneration of the lining cells. After seven days he found adhesions where the lining cells had entirely disappeared. Where they had regenerated there were no adhesions.

Dominici [11, 12] thinks the cellular part of the omentum is composed of several syncytiums; the syncytium of lining cells, of fibroblasts, of adventitial cells, of fat cells, etc. These syncytiums are not entirely separated from one another, but are connected by means of anastomoses between the cells. Scattered through the whole structure are free cells among which he classes the macrophages. These macrophages arise by differentiation from the various syncytiums which belong collectively to the connective-tissue series. According to him, the endothelial syncytium of lining cells is to be considered as modified connective tissue, which during inflammation gives rise to a large number of macrophages.

Von Büngner [4] thinks that both serosal lining cells and fibroblasts participate in the formation of granulation tissue, but he found that they retained their individual characteristics during the process, and that the cells derived from them could be easily differentiated into young connective-tissue elements and young lining cells. He could not detect any transition of lining cells into fibroblasts, but he thinks that the lining cells play a more important rôle in new tissue formation than is usually attributed to them.

Von Brunn,[2, 3] after minute study of inflammatory processes in the peritoneal cavity, concludes that the lining cells are of a specific epithelial type which never gives rise to fibroblasts and that young lining cells are never formed from fibroblasts during the processes of inflammation and the formation of new tissue. In referring to the work of the French authors he suggests that perhaps their views were so unanimously in support of a genetic relationship between lining cells and fibroblasts, because they based their conclusions principally upon observations made on spread preparations of the omentum, in which material, Von Brunn states, it is extremely difficult, if not impossible, to obtain a clear picture, the underlying fibroblasts becoming easily confused with the superimposed lining cells.

Tschaschin,[28,29] after a prolonged study of the serous cavities with vital dyes, concludes that the serosal cells, because they remain totally unstained, are specific; but in the omentum this specificity is extremely difficult to establish. In connection with this question it is interesting to note that he quotes Maximow as believing that the fibroblasts in the omentum and mesentery retain a more embryonic character than in the general connective tissues, and that it is more difficult to differentiate the fibroblasts from the resting wandering cells in the omentum than elsewhere.

Finally the work of Foot [14] on wound healing in the omentum must be referred to in this connection as it has a certain bearing on the results of these observations. In his experiments he found a very remarkable reversal of type in the case of the connective-tissue cells and of the endothelium to an undifferentiated mesenchyme, from which there arose new vessels, connective tissue, and "phagocytic endotheliocytes." These conclusions are of interest in regard to the relation of serosal lining cells to fibroblasts, because, if these two groups of cells are very closely related, it would seem most likely that the reactions described by Foot would involve the serosal lining cells as well as the connective-tissue cells.

In general, then, it seems that the majority of those investigators who have studied the omentum with particular regard to the question of the changes which take place during irritations have concluded that the fibro-

blastic and mesothelial elements are morphologically and functionally interchangeable. But this view has not been accepted by others, and the principal evidence in favor of the specificity of these cells has been obtained from the study of sections of the serosal membranes covering the various organs. The contradictory conclusions arrived at may have been the result of the various methods employed, or due to some fundamental differences between the cell potentialities as they appear in the omentum and in the general subserosal tissue, as suggested by Maximow.

It has been long known that the serosal lining cells underwent changes in size, shape, and general appearance when subjected to irritations. In attempting to determine the exact nature of these reactions it has seemed essential to reinvestigate both the omentum and the other serosal membranes with every available method. The reactions of the mesothelial cells are obviously important in two connections; the fundamental relation which they bear to the fibroblast and in regard to the rôle which they play in the formation of adhesions. The present communication reports the results of the examination of the omentum in an effort to determine whether the changes which occur in the morphological and cytological characteristics of the serosal lining cells, during mild irritations, indicate any genetic relationship, or functional similarity, between these cells and the fibroblasts.

The structure of the omentum of the rabbit is very characteristic. There is a framework of blood-vessels which anastomose freely without the intervention of a very elaborate capillary bed, that is, much of the circulation is arterio-venous in character. The larger vessels are surrounded by layers of adipose tissue and, in this way, the omentum presents the appearance of a flat membrane marked off by vessels and fat into irregular sections, or areas, of quite diverse sizes. Rich [23] has shown, however, that there is a capillary bed which is not apparent with the usual methods of observation, but which becomes very prominent after the administration of histamine, which by dilating the capillaries makes them far more conspicuous. But not even after the administration of histamine can a very elaborate plexus of capillaries be observed in the thin membranous areas ordinarily outlined by the larger and medium-sized vessels. That these areas are non-vascular is far from true, but the vascularity is sufficiently decreased at these places to make study of the membrane as a whole entirely satisfactory.

The thin membranous part of the omentum consists of numerous cells surrounded by a mass of interlacing connective tissue fibrils and covered by a layer of flattened mesothelial cells, whose outlines, in the normal state, can always be demonstrated by the mosaic pattern which they evidence after treatment with silver nitrate and subsequent exposure to sunlight. The special structures which are so evident in the omentum of the rabbit, called the tâches laiteuses, are scattered more or less indiscriminately throughout the entire omentum. The tâches laiteuses are collections of various types of free cells grouped about areas of increased vascularity. These cells have been widely studied in connection with the formation of free cells during inflammatory reactions in the peritoneal cavity, and in relation to general hæmatological problems.

The omenta upon which the observations reported here were made were from a series of rabbits which had had their peritoneal lining cells irritated by the injection of heterogeneous laked blood. Some of these rabbits were vitally stained by the intravenous administration of trypan blue, and a few received the vital dye intraperitoneally in order to give the irritated serosal lining cells every possible opportunity to absorb and store the dye.

When the animal was ready for study it was anæsthetized and the abdomen opened; the omentum was observed with regard to the general appearance, occurrence of adhesions etc. Several small pieces were transferred to coverslips, which were then immediately sealed to the slide with vaseline; these preparations were sometimes stained with neutral red by Pappenheim's method. In many cases small amounts of fluid were found in the peritoneal cavities of the rabbits and in such cases a small drop of this fluid was used to mount the fragment of omentum; in others Locke-Lewis solution or homologous serum was used.

The remainder of the membranous part was carefully spread without touching the surface, a coverslip was dropped on it and the area cut out; the coverslip with its layer of omentum was then immersed in a weak solution of silver nitrate for a few minutes, transferred to distilled water and exposed to direct sunlight until it showed a light brown; it was then fixed in 95% alcohol. Other preparations were rinsed carefully before being placed in silver nitrate, and still others were fixed immediately in alcohol, sublimate, or osmic vapor. From each animal at least three preparations were always made, one to be studied fresh, one silvered, and one fixed directly for control.

In the normal omentum, when the fresh preparation, the ordinary stained spread, and the spread treated with silver nitrate were compared, the remarkable fact was noted that in the two former the mesothelial layer of cells could not be made out at all. There were nuclei which were suggestive, but these were in no case sufficiently distinctive to be diagnostic. As soon, however, as silver nitrate was applied, the superficial layer became entirely apparent and distinctly separated from the other cells which were subjacent to it. It is entirely obvious that if in the normal, fresh omentum the cells could not be distinguished with ease, those in the irritated omen-

tum would be still more difficult to classify, so that the application of the silver method becomes even more important after irritation. In all studies on the fresh omentum it was impossible to determine the outline of the serosal lining cells, and hence the various types of cells present were very difficult to distinguish. In fresh unstained omenta from animals which had received two or three doses of laked blood the microscopic appearance was quite bewildering. In such a preparation only the nuclei and large numbers of granules surrounding them could be seen clearly. The cellular outline could be made out only in rare instances, and analysis of the type of cell depended entirely upon the appearance and reactions of their granular content. But by means of various vital and supravital dyes and by numerous control methods applied to the fixed material, the characteristics seen in the fresh could be analyzed to a considerable extent.

Three types of cells could always be observed. The first two were quite similar in many respects and were sharply differentiated from the third by certain characteristics of the vacuoles and granules which they contained. The two that resembled each other so closely had in common large, pale nuclei with one or two very highly refractive nucleoli, and contained varying numbers of highly refractive granules, all of which were of the same size and character. The arrangement and number of granules, however, within each cell permitted a division of these cells into two groups; one group having many granules which were usually distributed in one solid mass of quite varied shape, sometimes a crescent about one side of the nucleus, sometimes a belt surrounding the nucleus, and in a few cases they were arranged in several clumps about the nucleus. In all of the cells of this type the highly refractive granules were associated closely with the nucleus and were never seen branching out through the cell in any process-like arrangement. In the other type, this finding was just the reverse; the granules were scattered in quite irregular fashion from the nucleus, sometimes in a single, long, slender thread extending from each end of the nucleus, and again, in several irregular processes of uneven size and length, suggesting the spread legs of some arachnida. In this last type the granules were fewer in number and often formed very slender and detached threads extending throughout the finer processes of these cells. These two types of cells were, respectively, the serosal lining cells and the fibroblasts.

The third type of cell was the clasmatocyte, a cell whose character was indicated quite definitely by the great variation in the size of the vacuoles and granules which it contained. There were only a very few of the fine, highly refractive granules, but there were vacuoles of various sizes, and masses of hyaline material which were evidently phagocytic enclosures. The arrangement of these cellular enclosures was quite irregular, but seldom extended as in the fibroblast into fine lines or threads; they were rather blunt and rounded as though in true pseudopodia. Most of these cells were rounded, however, and appeared as balls or spheres of massed granules and vacuoles surrounding the nucleus.

When a preparation such as that described above was mounted on a coverslip previously prepared by being coated with neutral red, the three types of cells presented a very different appearance. The clasmatocytes took up large amounts of the dye into their vacuoles and became masses of red globules of different sizes with a few interspersed, fine clear granules; while the other two types had only a few, fine, red droplets scattered among the clear granules. In the fibroblasts there were more red bodies than in the serosal cells and they were especially prominent in small enlargements of the fine processes.

The application of silver nitrate to the study of the characteristics of the omental cells during inflammatory changes proved to be extremely difficult to carry out successfully, because it was found that a certain amount of fibrinous and cellular debris always accumulated on the surface of an irritated area and caused irregular staining with the silver. The use of silver nitrate to outline the margins of endothelial cells was first described by Von Recklinghausen [22] and has since proved a very important part of the technique in the study of blood-vessels and the linings of the serous cavities. What the nature of the reaction is, is yet in doubt. It was first thought to represent the impregnation of some intercellular cement substance which had the power of combining with the silver. It has since been suggested that the reaction was more likely due to a peripheral concentration of chlorides in the cells and that the silver oxychloride which is formed is reduced in sunlight so that metallic silver is precipitated in the borders of the cells. This entire question is thoroughly reviewed by Macallum.[17]

The cellular debris which is formed during the course of an inflammation increases as the intensity of the irritation is augmented, and in this way the application of the silver reaction to the irritated omentum becomes increasingly difficult. It must be noted here that the successful application of this method could not have been considered as plausible until the theory of peripheral salt concentration had been suggested. I have found that if the technique be carried out very carefully the method may be used to great advantage in the study of mildly irritated omenta. When the silver nitrate was applied in very weak solutions, ⅛ to ¼%, and the spread preparations were agitated gently while in the silver solution, and washed carefully before being exposed to the light, in some of the specimens the entire surface of each serosal cell had a brown appearance with a darker outline, and the entire layer of rounded or irregular cells became apparent. The use of this reaction to demonstrate

the stages in the changing mesothelial cells, during the progress of an irritation, has proved quite successful and has established certain definite characteristics as most specific.

The first change observed in the layer of serosal cells was an irregular widening of the line which marked their boundaries. This took place very irregularly so that there was no longer a perfect apposition of the cells each to each. In an omentum which had been subjected to a mild irritation there were many places where one could see groups of surface cells with perfect apposition, side by side with other groups in which considerable gaps occurred between the cell margins. This is shown in Figure 1; on the left of the figure there are several mesothelial cells which have outlines, changed only very slightly from the normal; while on the right the cells are beginning to separate and there are numerous spaces between them. This type of reaction is entirely natural in a structure like the omentum, because consistent changes could never be expected over the entire surface at one time. Every stage of separation of the cells from small gaps in the thin, continuous, brown line of silver precipitate, seen in the normal omentum, to areas the width of nuclei were observed, but in these early stages of irritation there were almost always points of contact except where an occasional cell had been desquamated. In many places the cells were bound together by numerous, fine processes as seen between the two cells shown in Figure 3.*

At the same time that the withdrawal of the borders of the cytoplasm of the serosal cells was taking place there was a beginning increase in the thickness and density of the cytoplasm. This rounding up of the serosal cells has been often observed in the serous membranes in general, but in the omentum the changing mesothelial cell has usually been confused with the branching fibroblast. The cells shown in Figure 2 have separated in part from each other and have increased somewhat in thickness but have not changed very materially from their normal, flat morphology. Here and there in early stages a single cell was found to have been desquamated and a larger area than could have been formed by mere separation was discovered, but other places were to be seen in every preparation where the cells were regularly spaced as if they had each retained their normal positions and merely had become more and more rounded up. In these early stages of irritation the processes which the serosal lining cells manifested were very striking and were quite characteristic, varying from cell to cell only in the matter of size. They were seldom very long, though they occasionally reached 8 to 10 microns in length. They were sharply pointed, somewhat similar in shape to the old-style church steeple. They generally extended at right angles to a line drawn at their base tangential to the periphery of the cell, and in cases of more rectangular cells were perpendicular to the sides. These projections were usually fine, very sharply-pointed, and about 3 to 5 microns long, although, as already stated, they were sometimes even longer. Very occasionally the ends were blunt or forked instead of pointed, but this was not very common, and neither did these processes have bulbous enlargements on them, nor were they divided to form two, definite, characteristic branches. These processes are well illustrated in Figures 2, 3 and 4. Figure 3 is a microphotograph of a preparation in which a large rectangular cell was becoming separated from a smaller one, and the processes which still hold them together are well shown. In Figure 2 there are to be seen the fine, long processes characteristic of cells which have but recently separated from each other. It is important to note here that almost every individual preparation of an omentum from an animal with relatively mild peritoneal irritation showed several stages of the progressive changes which represented the course of an irritation. This is easily understood because the omentum may be exposed in part, and protected in part at the same time. In every specimen, however, there was a general preponderance of a certain type, and in this way it was easy to establish the characteristics which represented the several different stages in the process. I mention this because it is so very easy to misinterpret histological appearances and it is essential to be assured that the particular area which is being examined represents a definite stage in the series of events which are being studied.

In the stage following the one described above the mesothelial cells had continued their increase in thickness and the rounding up of their cytoplasm, and therefore the edges of the cells were more widely separated. As this rounding up progressed, the number of processes on the cells diminished in number, but those that remained were in general somewhat larger. One cell in Figure 4 has a process of this type. In this stage of the irritation the omentum was often covered in large areas

* This brings up the question of whether the surface cells form a true syncytium, as claimed by Kolossow, or whether these cells are merely in apposition, as is the case with many tissues. Kolossow[16] describes the lower part of the serosal cells as anastomosing with the neighboring cells by means of fine processes, while the upper part of the cell merely lies in apposition to the surrounding cells. If this opinion prove correct, it will be easy to understand the drawing apart of cells with the formation of multiple, small openings between the anastomosing processes. It is evident that the observations cited above, at first sight, strongly support Kolossow's idea that the surface cells are bound together by numerous processes. But long and careful study of large numbers of preparations has not convinced me that these are anastomoses in the sense of syncytia, but rather served to indicate a union of a less intimate character. There is, however, very little doubt but that there is some type of junction which binds these cells together more closely in some places than in others. The nature of this union has so far not been analyzed, and is a most difficult question to settle.

by cells scattered very regularly, but separated from each other by quite considerable areas of denuded tissue. Figure 4 is from such an area and here it is quite certain that no cells have been desquamated. In Figure 3 it is probable that cells have been desquamated, as the distances between the cells appear greater than usual for so early a stage. In preparations from animals which had been exposed to still longer irritations the mesothelial cells had rounded up still further, they had been desquamated in a greater degree, and were in large measure obscured by the numerous clasmatocytes which had reached the surface and were adhering to it, as well as by some cellular debris. The processes of the serosal cells had not materially changed in type, but were somewhat more irregular than in earlier stages, probably due to the attempt of some cells to flatten out and recover the denuded areas while others were continuing to round up as the result of the continued irritation. Mitotic figures were extremely difficult to find in preparations of spread omenta, and the evidence of cellular division was based upon sections taken from the same omenta and appropriately stained. Active mitotic figures were relatively few even in these sections but many cells were to be seen in various stages of division.

When the silver preparations are successful, they are very brilliant and demonstrate that the morphological changes which take place in the mesothelial cells are wholly characteristic and indicate the specificity of this cell-type. When the technique outlined above was combined with previous vital staining the definition of the serosal lining cell as a specific type became even more exact, since the method of storing the vital dye was equally as specific as the morphological changes.

In all of the omenta from animals vitally stained with trypan blue, the mesothelial cells showed very interesting reactions. In the normal these cells have been found to store the dye in a rather characteristic manner, the dye being collected in a small clump in a definite part of the cell; on progressively increased staining the dye-granules extended around the nucleus in a perinuclear rosette. The normal staining of the serosal lining cells has been described in detail elsewhere.[10] Studying the reaction of the cells which had been irritated, the deposits of blue were found to deviate somewhat from those in the normal. As the cells began to separate and round up there was a tendency of the blue droplets, which had been rather specifically located in one end of the cell, to be dispersed somewhat more widely in the same general part of the cell. In Figure 2 the blue granules can be seen as groups of definite black spots in one end of each cell, *i.e.* opposite one pole of the oval nucleus. But the granules are somewhat irregular in distribution, as may be noted especially well in the two cells in the lower right corner of the photograph. The silver precipitate in a large measure obscures the blue granules in the bodies of the cells. With increased irritation there was a more general tendency to even distribution in those parts of the cell where there was much blue and a gradual though uneven widening of the belt of blue constituting the perinuclear rosette. In general the effect of irritation was found to be a more even distribution over a larger area of cytoplasm, sometimes but not always, accompanied by a diminution in the concentration in that part of the cell which originally contained a small ring or mass of granules. In Figure 5, which is from an omental spread that had been treated with osmic acid and had not been silvered, there is, in the upper center, just above the round, heavily stained clasmatocyte, a mesothelial cell which is somewhat out of focus, but which nevertheless illustrates the distribution of the vital dye granules as irritation progresses. The cell is irregularly triangular in shape, the upper part on the left being entirely out of focus, while in the upper right there is a very distinct ring of blue granules. This ring represents the first dye deposited in the cell while the patches of granules in the remainder of the cell have been formed during the progress of the irritation.

It is extremely important to note that in no case were there any granules of blue to be seen in the processes of the serosal cells. In fact, in those cells having the largest processes there was not the least tendency of the blue granules to enter them, and in this particular there was a very sharp contrast to the fibroblasts. In Figure 4 there are two cells which have very characteristic processes, and these show very clearly that they contain no dye inclusions. These clear processes should be contrasted with the long, branching, dye-filled processes of the fibroblasts in Figures 5 and 6.

The reactions of the fibroblasts and the clasmatocytes in these omenta from animals having mild irritations were wholly characteristic. Scattered throughout the omentum characteristic fibroblasts were to be found everywhere. The typical fibroblast has been studied and described so often that it seems useless to enter into the especial characteristics of this cell at any length. Schott,[26] Büttner,[5] Kiyono[15] and Tschaschin[28, 29] have figured the fibroblasts in the omentum as large cells with smaller nuclei than the serosal cells, fading outlines, and fibrillary cytoplasm. Evans and Scott[13] have studied them in subcutaneous preparations with numerous vital dyes and figure their vital dye content quite extensively; it is probable that these would be similar in the omental fibroblasts, even though Maximow has suggested that they retain their embryonic characteristics in this locality during adult life. In preparations from a normal omentum which has been vitally stained with trypan blue and then silvered, the fibroblasts were seen in between the two layers of serosal cells as faintly outlined cells with fine blue granules scattered through the cyto-

plasm. These cells were often branched and even though the outlines were difficult to indentify exactly, they could be made out to some extent because the trypan blue was distributed throughout the processes. When subjected to the effects of irritation, the fibroblasts instead of becoming more compact developed much more extensive processes which in many cases were quite remarkable. They reminded one very much of the branched cells of the tadpole's tail as figured by Clark and Clark [7] and in a quite similar manner contained the trypan blue in those enlargements which are found on their processes. In my preparations these cells were especially characterized by the fact that the vital dye extended to the tips of their branches (Fig. 5), although the amount of dye in the fibroblast was very much less than that found in the clasmatocyte. As has been stated, the fibroblasts lie scattered throughout a meshwork of fibrils between the layers of serosal cells. During early stages of any irritation these two groups of cells undergo specific changes without much departure from their definite layer-like arrangement. The mesothelial cells of the entire surface layer have, in many omenta, separated and rounded up, so that each cell was divided from its neighbor by a considerable area; and at a different level there were large numbers of variously shaped, richly branching fibroblasts. This layer arrangement is well illustrated in Figures 4 and 6. Both are photographs from the same omental spread. In Fgure 4 there are shown seven mesothelial cells which have separated from each other and rounded up to a considerable degree; if the photograph be studied carefully the shadows of other cells can be seen in the depths. In Figure 6 the camera was focused on the fibroblastic layer and the mesothelial cells may only be seen as faint outlines; one of these can be fairly well made out in the lower left corner, while two others cast somewhat less well defined shadows in the upper right corner. When the irritation was more advanced there was more tendency for arms of the branched fibroblasts to extend into the spaces between the separated mesothelial cells. In Figure 5 the single mesothelial cell is seen to be only slightly out of focus, while there is considerable variation in the relative clearness of the different processes of the two numerously branched fibroblasts. The distribution of the dye in these long, fine, streaming processes was most remarkable, some of them extending entirely across the oil-immersion field, and often they appeared to be attached to or following fibrils of some kind. The contrast between the fibroblasts and the clasmatocytes in Figures 5 and 6 is very striking, particularly in Figure 5; and it must be noted that the characteristics are about equally as specific for the two types of cells in both figures.

In the omentum of a vitally stained rabbit there are, in addition to the fibroblasts, many large cells, most of them long and narrow and loaded with blue granules. Among these cells are some that are round or oval in shape; these latter are especially numerous in the tâches laiteuses. These cells are typical clasmatocytes and have been carefully studied by many observers. Marchand [19] notes their especial affinity for the perivascular regions and calls them "adventitial" cells. Long lines of them are always arranged along the course of blood-vessels and are at times in most intimate contact with the endothelium of the capillaries. This distribution of the clasmatocytes is used by Shipley [27] as an argument for concluding that they represent a type of digestive organ, functioning intermediately between the blood-vessels and the tissue-cells proper. In preparations of the normal omentum the clasmatocytes were usually either long and slender cells with centrally located nuclei, or else round or oval cells with somewhat excentric nuclei. The former type is the one invariably associated with the blood-vessels, and so striking is this morphology that they have been termed "trailer" cells by Buxton and Torrey.[6] In the tâches laiteuses the more compact type was often met with, but even here, there were large numbers of the long and slender cells loaded in a striking manner with the vital dye.

When the omentum was irritated, the first change that could be noted in the clasmatocytes was a tendency to round up and change from the long, slender cells to round or oval masses, with or without, short, blunt processes. The surface of any irritated omentum was dotted with these round cells loaded with trypan blue and large numbers could be seen between the serosal layers. Figure 5 shows the typical rounded clasmatocyte, while Figure 6 shows one with blunt processes filled with trypan blue inclosures.

In the study of the omentum during mild irritations by means of the methods outlined above, it has become entirely clear that the serosal lining cells and the fibroblasts react differently both as regards their morphological appearance and the distribution of their vital dye-content. The serosal lining cells increase in thickness and are much more compact than the normal, flat, plate-like structures. They differ considerably in size and shape, being round, oval or square and some of them have a few, fine-pointed processes which vary in size but not in character. The vital dye content is more diffuse than in the normal cells, but there is never any dye to be seen in any of the fine processes. On the other hand, the fibroblast during irritation becomes an elaborately branched structure, forming a marked contrast to the compact serosal cell. The processes of the fibroblasts vary enormously in size and shape; some are long and slender, others branched into two or more subdivisions, and many have bulb-like enlargements, especially where they branch. The vital dye is distributed throughout these processes, the granules often being collected in the bulb-like enlargements.

It is thus obvious that during the course of a mild irritation the changes which take place in the mesothelial and fibroblastic elements indicate that they become even more widely separated from each other in their group-characteristics. The cell-bodies and processes of these two cell-species are morphologically quite distinct in regard to size, shape and general characteristics. It seems entirely justifiable to conclude that such marked differences must denote some variation in the structure of the cytoplasm, and hence indicate some especial adaptation for certain definite physiological activities. In addition to these morphological criteria, it has been demonstrated that the vital dye content of the fibroblast and the mesothelial cell presents a sharp contrast. Here again the principal interest is attached to the wide distribution of dye granules in the processes of the one cell and the total absence of the dye from those of the other. That differences in the way in which vital dyes are stored represent corresponding differences in physiological adaptation seems most probable, and permits further security to be placed in the conclusion that the mesothelial and fibroblastic elements are wholly specific.

It is hoped that the observations reported above, which differentiate the reactions of the mesothelial cell and the fibroblast quite sharply during mild irritations, will be useful in determining the rôles performed by each of these two types of cells in the healing of wounds, the regeneration of denuded areas, the formation of adhesions, and finally aid in establishing the genetic derivation of the so-called "endotheliomata" of the lining membranes of the various serous cavities.

## EXPLANATION OF PLATE

All the figures are micro-photographs of omental spreads from rabbits which had had continuous, mild irritations induced by the repeated introduction of laked blood into their peritoneal cavities. The negatives have not been retouched.

Fig. 1.—Exposure to mild irritation for 36 hours. Preparation silvered and stained with carmine. Shows relatively normal mosaic pattern on the left, and beginning separation of the cells on the right. x 500.

Fig. 2.—Exposure to irritation for 60 hours. Preparation from rabbit which had been vitally stained with trypan blue. Silvered and stained with carmine. Shows partial separation and beginning rounding up of the mesothelial cells. The blue droplets are seen as irregular patches in the cells. x 700.

Fig. 3.—Exposure to mild irritation for 4 days. Silvered and stained with carmine. Shows the final stage in the separation of two mesothelial cells and the general characteristics of these cells when definitely modified by the irritation. x 1100.

Fig. 4.—Exposure to mild irritation for 5 days. Vitally stained with trypan blue. Shows the even distribution of the serosal cells on the surface of the omentum; there has probably been no desquamation. x 850.

Fig. 5.—Exposure to mild irritation for 6 days. Vitally stained with trypan blue. Fixed in osmic acid and stained with carmine. Shows two clasmatocytes heavily loaded with blue granules, two branching fibroblasts, and one mesothelial cell. x 700.

Fig. 6.—Same preparation as Fig. 4. Shows one clasmatocyte with a large content of trypan blue and pseudopodial-like processes, one characteristically branched fibroblast, and the shadows of three mesothelial cells which are out of focus. x 750.

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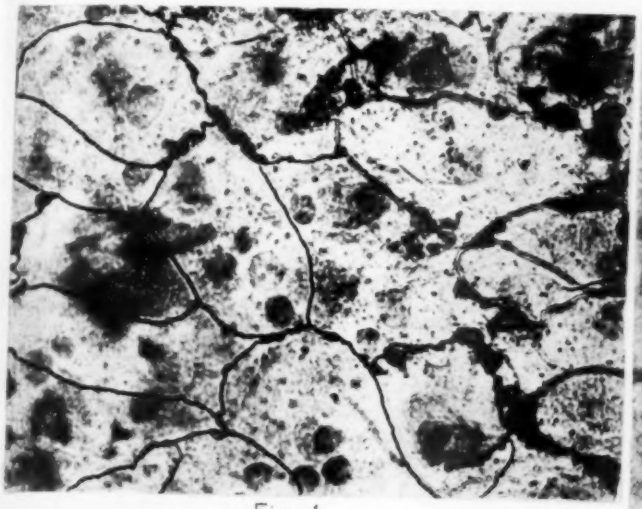
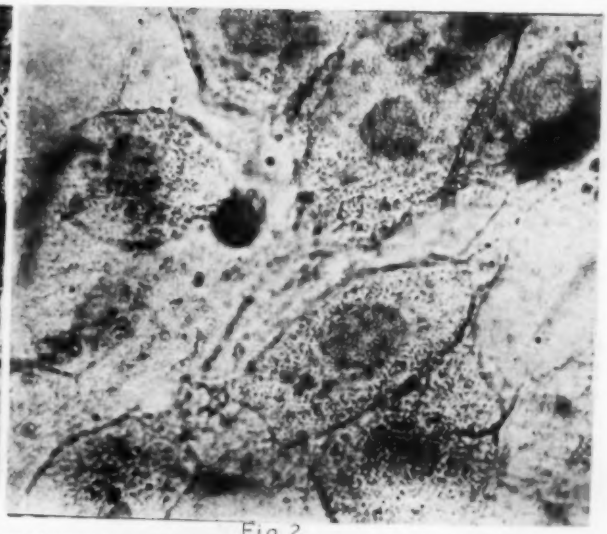


Fig. 1



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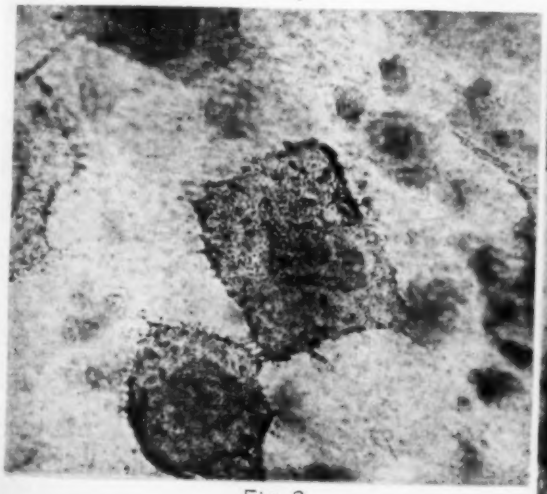

Fig. 3

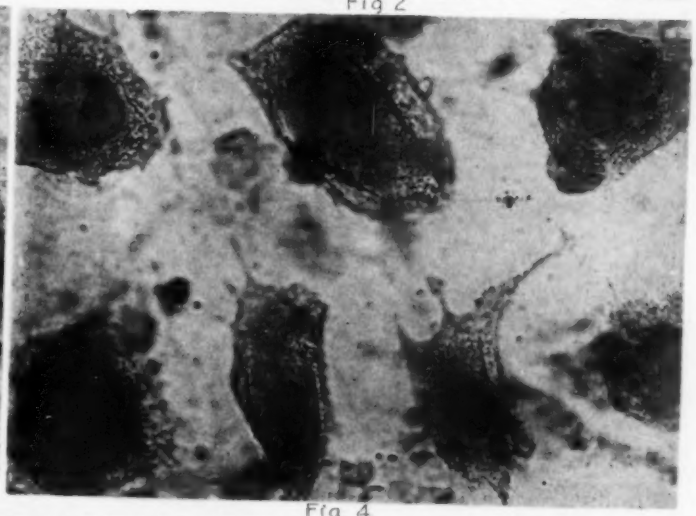

Fig. 4

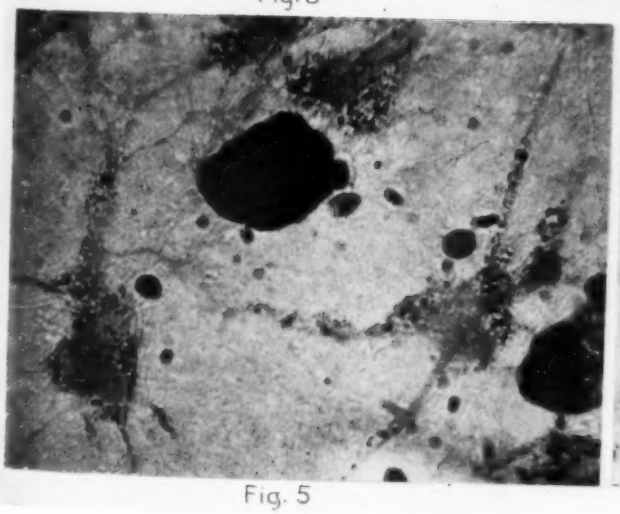

Fig. 5

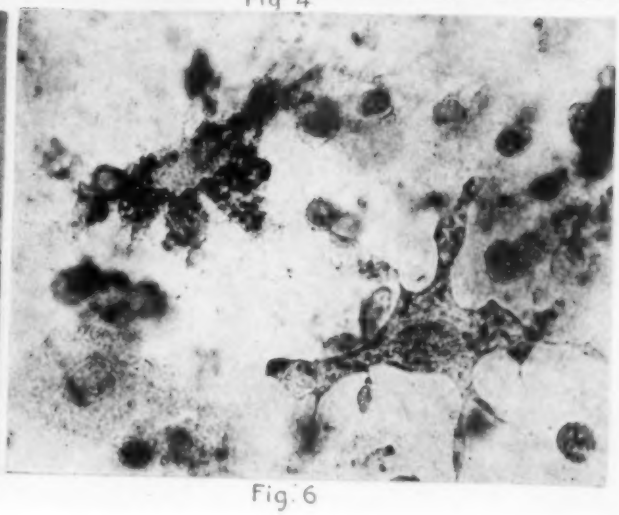

Fig. 6

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# THE ELEMENTARY SCHOOL AND THE INDIVIDUAL CHILD *

## (ABSTRACT)

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In Mental Hygiene for April, 1920, the writer described a fifteen months' study of "Some Adaptive Difficulties Found in School Children." The work was a bit of private research in School No. 76 of the Baltimore schools, and quite divorced from any organized activity in the public school system.

Of the forty-six children who came under observation, thirty-five were reported as having difficulty in keeping up with their grades in one or more subjects. In each of these cases where there was a suggestion of retardation, the Binet-Simon test was applied. As a result, sixteen of the above-mentioned thirty-five were found to have a mental retardation of from three to six years. The academic troubles of the remaining nineteen were associated with, if not the disguised expression of, such faulty psychobiological reactions as shyness, laziness, inattention, and vicious tendencies, sensitiveness to criticism, daydreaming, hypochondriacal fears, with resulting irregular attendance. The eleven remaining from the total forty-six were referred for the more overt adaptive difficulties of temper tantrums, sullenness, crying spells, twitching, indifference, excitability, poor coordination with the hands, quarrelsomeness, etc.

In reviewing the data accumulated, one fact stood out; in practically every case the peculiar characteristics for which the child was referred could be easily traced to their first appearance in the early years of school-kindergarten and first and second grades. In the majority of cases, also, the unhealthy habits of adaptation began in the home, and were carried into and through the school life, handicapping the efforts of teacher and child to get together on the business of early training in the classroom; and the commonest result of this handicapping was the repetition of grades. Accordingly, it seemed best to devote some time to the first grade, with the special object of examining the problem of backwardness at its source.

By way of experiment, eighteen children were selected from the first grade for special study. Their ages ranged from six to ten, and their years of repeating the first grade from one to three. These children were studied from the standpoint of the story of the home, the story of the school, and the story of the child himself, as recorded under the headings of complaint, school history, habit data, personality traits, and a rough estimate of physical status as obtained from the health records, weight curve, and brief examination. Aside from the Binet-Simon tests, no special technique was used, either in the examination of the children or in the sifting of facts. The Binet-Simon findings were as follows: In two cases the actual age and tested age were exactly the same; in seven cases there was a difference of only one year between the actual age and the tested age; in seven cases there was a difference of two years between the actual age and the tested age; one child objected so violently to examination that it was thought best not to push matters; and one child showed a difference of three years between the actual age and the tested age. It was felt that the difference of from one to two years between the actual age and tested age of fourteen of these

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children represented no real backwardness, but was the expression of various factors in the background, development, early training, and personality traits of the individual children. That these were the facts responsible for the lodging in the first grade seemed more probable than deficient mental equipment.

Turning from the facts of standardization to those of physical condition and living arrangements, there was nothing striking in the story of these little people. There was one mouth breather, one child with definite eye strain, and two tuberculosis suspects. Several children appeared pale and undernourished, but only two weight curves were below the normal. The habit data were characteristic of this industrial section—comparatively late bedtime, with two, often three sleeping in a bed; a diet of coffee, buns, and soup; movies two nights a week. Unideal as these conditions are, it must be remembered that they have not proved a serious hindrance to the school progress of hundreds of other boys and girls.

These eighteen candidates for reconstructive therapy were put under a special teacher in September, 1920. In June, 1921, ten members of this class were qualified for the third grade and seven for the second grade. Only one child of the class failed to respond to special study.

To what have these results been due? Before giving my own impression of the matter, let me say a word about the school background of the above experiment. For several years School 76 has been studying the problem of repetition in its midst. For three years a special health worker, privately financed, devoted her whole time to following up minor ailments—common colds, post-contagious-disease conditions, and any other factor influencing regular attendance. The result was an attendance record of from 96 to 98 per cent, but the repeating of grades remained *in statu quo*. This same worker directed a campaign towards the relation between progress in school and the clearing up of tonsils and adenoids. The results, over a period of three years, were that 50 per cent of the children operated on showed no difference in their school work, 25 per cent showed some improvement, and 25 per cent appeared to make a poorer showing than before operation.

The plan tried in the first three grades of dividing the class so that each half of a room rotates between playground and class work resulted in a certain amount of gain in school progress, due to the fact that each teacher worked with smaller groups. It did not, however, eliminate repeaters such as have been described above, the majority of whom had been accorded the benefit of the scheme just outlined.

In view of these facts, it would seem that the success obtained with the experimental class was due not so much to the extra time spent on them as to the fact that this time was devoted to a study of the individual needs of these children. Here were eighteen school failures according to the criterion of grading, and eighteen individuals whose pedagogical record and Binet-Simon findings would be credentials enough to admit them without question to that mysterious order called "the backward child." They could not be poured into the ordinary mold of school curriculum because of certain traits of personality that had to be discovered, understood, and wisely handled. The same psychobiological characteristics of shyness, indolence, fear, sensitiveness, daydreaming, etc., acted as conflicting factors in the Binet-Simon tests, obscuring the native capacity to such an extent that a difference of from one to three years appeared between the child's actual age and tested age.

A year of school training directed by an understanding of these characteristics has resulted in restandardization data with the Binet-Simon tests in June, 1921, that run parallel with the academic progress of these children as recorded in their grading reported above. The seven children who showed a difference of two years and over between their chronological age and mental age according to intelligence tests made in March, 1920, now show a mental level that coincides with their actual physical age.

And for those of us who examine such children, there is subject for reflection. Are we using the Binet-Simon scale as a yardstick to measure off lengths of intelligence, or are we using the tests as a help towards the sizing up of individual child problems? Are we confusing the term "mental age" with a diagnosis of the home situation in question? Do we see the personality with its setting of life story behind the intelligence level? These are possibilities of view that at times seem strangely remote from the productions of psychiatrists and practicing psychologists. As such, we should beware of agitating ourselves to decimal points of determination concerning qualifications for the groups of subnormal and dull, lest the object of our research becomes buried beneath the mound of his own case.

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# NOTES ON NEW BOOKS

*Studies in the Paleopathology of Egypt.* By SIR MARC ARMAND RUFFER. Cloth, $7.50. (*University of Chicago Press, 1921.*)

This is a collection of Sir Armand Ruffer's papers published after his death evidently with the loving aid of Lady Ruffer who worked over many incomplete manuscripts and brought together notes and literary references to complete them. The papers treat of an extraordinary material so romantic as to compel the interest of everyone to whom the names of Thutmose, Amenhotep and Rameses call up the ancient glory of Egypt.

The author had great opportunities for the study of the mummies of all the periods of Egyptian history and utilized them for the purpose of determining the character of the diseases from which the people suffered. This was relatively simple in the case of bony lesions, among which various forms of osteoarthritis deformans stand out prominently. Spondylitis with bony ankylosis of many vertebræ seems to have been common and periarticular exostosis hardly less so. Tuberculosis occurred and there is a case of Pott's disease with a psoas abscess, but there were no evidences of syphilis. The teeth furnish also much accurate information and it is readily seen that the ancient people took little care of them and that there were no efficient dentists. The teeth were often greatly worn and in an advanced state of caries with destructive abscesses which martyrised with toothache even such an exalted person as Amenhotep III.

It was found that the soft tissues of these mummies, although dried into unrecognisable form, could be softened and made pliable and even embedded in paraffin so that microscopical sections could be cut and stained. The tissues are by no means destroyed and cells can be recognised with their nuclei; muscle fibres with striations, elastic fibrils, areas of calcification and even bacteria and the eggs of Bilharzia hæmatobia can be clearly seen. The methods of embalming which are fully described were such as to destroy many of the tissues, often leaving others tightly wrapped round little statuettes which were placed in the body. The arteries were not used for injection of fluid, but were slashed away everywhere, and even most of the muscles were removed and replaced by all sorts of material. But although no connected examination of all the organs could be made, isolated observations of extreme arteriosclerosis, cirrhosis of the liver and renal disease were frequently possible.

Dwarfs, including some which were evidently chondrodystrophic, and various malformed persons are unmistakably recorded in the ancient sculptures. The Queen of Punt looks as though she were the victim of congenital dislocation of the hips rather than rickets or elephantiasis.

There are various other studies such as that of a lower miocene crocodile with arthritis, an osteosarcoma of the pelvis, a variola-like eruption of the skin together with many nondescript ulcers and wounds, the traces of which remain and sometimes, as in the case of Saknounra, throw some light on history. These diseases are largely repeated in the case of the Copts, the Sudanese and the Nubians.

Most interesting are the studies of the Royal mummies which are, however, rather restricted owing to the divinity which hedges around these personages even now as they lie in the Cairo Museum. Everyone who has dwelt with pleasure upon the portrait busts of Ikhnaton, with their eager yet dreamy delicacy, must feel a shock of disappointment upon learning that he was a ridiculously obese man even in a household where all the members were very stout. The rest seems not very important. Rameses II was bald and had blackheads on his forehead. Thuthmose III and Amenhotep II had a macular eruption on their legs, and two or three queens were bald.

On the whole though, they were pretty well—all these royal people—and in spite of their consanguineous marriages they were preeminently strong, fertile, intelligent and vicious.

It is an extremely interesting account in spite of the rather wearisome repetitions, which are perhaps unavoidable in a collection of papers published at considerable intervals, and one is impressed by the infinite pains required, in handling these crumbling remains, to snatch from oblivion a few meagre hints of the discomforts and sufferings of these vivid people of thousands of years ago.

W. G. M.

*The Care of the Eyes.* By ROBERT HENRY ELLIOTT, M.D., B.S., Sc.D., F. R. C. S. (Eng.). (*London, Henry Frowde and Hodder & Stoughton, 1921.*)

This book is an elementary treatise, intended especially for nurses, on the subject of ophthalmic nursing and diseases of the eye. Of the three sections into which it is divided, the first deals with the special anatomy and the general and special therapeutic procedures used in ophthalmology. The second part contains a very brief description of the commoner diseases of the eye. The third, in the form of an appendix, is probably the most valuable section of the book It illustrates the special instruments used in eye surgery, and gives excellent lists of those employed in the various operations.

Inasmuch as various ophthalmic clinics develop individual technique, nursing and therapeutic procedures within fairly wide general limits, the general value of any treatise, which outlines the technique and nursing procedures used in one individual clinic, will not be great. There are, however, many excellent chapters, and many essential points clearly made, which are of undoubted value. The second part of the book, dealing with diseases of the eye, is too brief. The appendix, describing instruments and lay-outs for various operations, is unusually complete. With such minor additions as any surgeon would make to suit his own individual preferences, this section will be of distinct value to the operating room nurse.

The book is well gotten up and quite readable.

A. C. W.

*Obstetrics and Gynæcology.* Edited by JOHN S. FAIRBAIRN. Cloth, $20.00. (*London: Oxford University Press, January, 1921.*)

The purpose of this book is evidently the very laudable one of bringing together in one volume the subjects of obstetrics and gynecology. This is in accord with the growing opinion that the two subjects are so closely related that the successful practice of one requires a thorough knowledge of the other. The arrangement of the subject matter is excellent and is proof that no sharp line of separation can be drawn between the two branches. The editor has wisely included many topics, such as public health and social and medico-legal problems, which are ignored in most texts.

Although this volume is the work of fifty-five authors, there is remarkably little overlapping of description and discussion. However, of necessity each topic is brief, and therein lies the chief weakness of the book. This brevity limits the mention and discussion of varying opinions to a minimum and, in many instances, to a more or less dogmatic expression of the author's individual views. This is particularly true of the sections on operative procedures.

It is unfortunate that the illustrations are so inadequate. More of them would be helpful, and many of those used are so reduced in size as markedly to limit their value.

J. W. H.

*The Treatment of Common Female Ailments.* By Frederick John McCann, M.B., M.R.C.P., F.R.C.S. (*Edward Arnold & Co., London, 1922.*) 145 pp. $3.00.

This book of one hundred and forty-five pages has been written to guide the general practitioner in the general care of gynecological patients. The author deals with the various subjects in a concise and practical manner, giving many useful hints and prescriptions and covering a phase of gynecology which is too often overlooked by the modern specialist.

In spite of its merits, this little book is open to several criticisms. Like most works of this sort, it leaves one unsatisfied. The physician who is acquainted with the fundamental principles of gynecology usually does not need such an elementary text, and one who does not possess this acquaintance, needs far more. In the second place, we question the advisability of including in such a work decriptions of technical procedures such as the performance of operations, and the administration of radium, or the extended discussion of abstruse subjects like endocrinology, all of which are attempted in this manual. Furthermore, we feel that the author has been unfortunate in recommending certain procedures which seem to be antiquated, while failing to mention some of the noteworthy recent contributions. In general, although this book contains much that is practical and useful, it may prove disappointing to the practitioner who needs an up-to-date guide in the treatment of genito-urinary diseases in women.

L. R. W.

*Syphilis and Its Treatment.* Wilfrid S. Fox, M.A., M.D. Cloth, $9.00. (*New York, Paul B. Hoeber, 1921.*)

In this work intended for the use of medical students and practitioners of medicine, the author has limited himself chiefly to a discussion of the skin lesions of the disease. The illustrations consist of numerous water color and black and white drawings. There are few references to recent or remote literature, and the material represents the personal experiences of the author, treated in an informal way. Partly for this reason, but chiefly because the book presents only one side of the disease—and that perhaps the least important, from the standpoint of the patient—it falls far short of being a desirable text for students. Many writers on syphilis inadvertently (or purposely, as in this instance) fail to deal with syphilis as a disease affecting all portions of the bodily mechanism and stress only its manifestations as applied to certain organs or systems. This method of handling the subject, while satisfactory for those already expert in syphilology, is distinctly a faulty approach for the novice.

The text contains many rather dogmatic statements which either overlook the established facts or are not substantiated by them. For example, it is stated that except in monkeys, animal "inoculation experiments have been negative or doubtful. In rabbits there is a disease nearly related to it, if not identical, and Noguchi claims to have inoculated the testicles of rabbits with syphilis." The existence of true rabbit syphilis has of course been thoroughly established by many observers, chief among whom are Neisser, Uhlenhuth and Mulzer, Nichols and Reasoner, and Brown and Pearce. The statement that mercury given by inunction is absorbed in considerable quantities through the lungs by inhalation is hardly in accord with known facts. The discussion of the paternal transmission of syphilis, will meet with many objections from the syphilologists of this country. The failure to mention routine spinal puncture as an indispensable accompaniment of the management of early syphilis constitutes a grave omission.

J. E. M.

*Heart Disease and Pregnancy.* By Sir James Mackenzie. (*London, Henry Frowde, and Hodder & Stoughton, 1921.*)

This small volume adds another to the list of works bearing the impress of the long clinical experience and research of the distinguished author, and has all the interest and charm one has learned to expect from the writings of Sir James Mackenzie.

While essentially a restatement of the newer knowledge of cardiac disease, as so often emphasized by the author, it constitutes an appeal for the application of this knowledge to all the problems relating to the question of marriage and the dangers involved in pregnancy and confinement for women the subjects of cardiac disease.

Written with the purpose of presenting his own views, based upon a long personal experience, to the obstetrician as the individual vitally concerned, one can not help feeling that the author has failed to appreciate, in a measure at least, the real extent to which the modern knowledge of cardiac disease has been made familiar to the obstetricians as well as to the profession generally. That just such a statement of the underlying principles involved will, however, prove of great value to many cannot be denied.

It is refreshing to read the author's description of the sequence of events in mitral stenosis of rheumatic origin and to get in his clearly put words the statement of the method for the correct evaluation of the physical signs in this condition as well as in aortic insufficiency. The chapter devoted to the neurotic heart covers this phase of the subject in a most satisfactory way.

Although lacking any exhaustive discussion of a number of points involving the pathological physiology concerned, and dealing chiefly with the clinical phases of the subject, there can be no question of the soundness of the views advanced.

A very complete index adds much to the value of the volume.

E. P. C.

*Diseases of the Eye.* By George E. De Schweinitz, 9th Edition. (*Philadelphia and London, W. B. Saunders, 1921.*)

That De Schweinitz' "Diseases of the Eye" has reached a ninth edition is a sufficient proof of its merit. In a book of this kind it is very difficult to meet the wants of everyone. Nevertheless, all in all, even the most critical should be satisfied. The revision of certain parts of the book and the foot-notes add materially to its value. The new edition is up-to-date, and includes a discussion of the more recent subjects in Ophthalmology—Localization and Organization of the Cortical Centers of Vision, The Dermic Grafts, The Epithelial Inlays, Jennings' Self Recording Tests for Color Blindness, Ophthalmoscopy with Red Free Light, Electric Desiccations, etc. Credit is given to other authors for their work or suggestions. In fine, Dr. De Schweinitz has given us another book which will render good service to the practising Ophthalmologist and the special student.

L. J. G.

*Epidemiology and Public Health.* By VICTOR C. VAUGHAN, HENRY F. VAUGHAN and GEORGE T. PALMER. Cloth, $9.00. (*St. Louis, C. V. Mosby Company, 1922.*)

Progress in the study of infectious disease has been marked by a series of disappointments in the application of specific therapeutic measures following the early brilliant successes in diphtheria and meningitis. Today the immunologist concerns himself largely with matters only remotely related to the practical management of disease; the actual fight has been left to the epidemiologist and the public health worker. We lay more and more stress on the prevention of disease as a whole, as well as in the individual, and the recent blight, especially, cast by the influenza pandemic has impressed on those concerned with the health of the nation the essential importance of understanding and grappling with the conditions which underlie and promote the occurrence of such scourges.

It is with interest, therefore, that one approaches the new work on Epidemiology and Public Health by Victor C. Vaughan of which the first volume on Respiratory Infections is before us. After reading this section which contains an excellent summary, both of the historical development and of the contemporary status of epidemiological ideas, one feels that an era is closing. Despite the vast amount that has been accomplished, the hope of the future seems fully as great as the performance of the past. It becomes clear that with no more than our present knowledge the next influenza epidemic will blast us like the last; poliomyelitis and encephalitis are as baffling as ever from the standpoint of prevention, and in tuberculosis the ground is barely cleared for rational and concerted attack. The interesting fact that healthy carriers may harbor pneumococci or meningococci or diphtheria bacilli has as yet led to no fruitful practical method of checking epidemics due to these organisms. Epidemiology, in short, has thus far brought out mainly generalities about the spread and incidence of disease. In the succeeding era it may be hoped that the application, still incomplete and abortive, of these generalities will mature into a practical and certain control of the scourges yet unchecked.

In summary, Vaughan's book states the problem and brings it up to date, the dry facts being varied by sections in which the author's well-known ideas on the "protein poison" are elaborated.

A. L. B.

*Human Parasitology.* By DAMASO RIVAS, B.S.Boil., M.S., M.D., Ph.D. (1st edition, *W. B. Saunders Company, Philadelphia and London, 1920.* 715 pages, 422 figures, 18 plates.)

The reviewer purchased this book with a sense of comfort in having discovered the long needed comprehensive English treatise on parasitology. The appearance of the book is attractive and its size seemed designed to permit a certain degree of completeness. It was a pleasure to note in the preface that the author had "kept himself informed of changes in nomenclature" and was aware of the fact that "the ever changing nomenclature of parasitology is a continued source of embarrassment." This seemed to promise a discriminating criticism of the names given to parasites, and the adherence to valid terms.

This prefatory satisfaction, however, was not long sustained. In the text for Fig. 12, "linen threads" are noted in the diagram of the cell, and at this point the reader picks up a strand of error which runs through the fabric of the book. This, like the word "amiboid" on p. 606, may have been a typographical error. Throughout the book, however, there are many similar examples of inaccurate uses of words, uncritical compilations and contradictions. An insect is at one time described as the intermediate host, and at another the definitive host, of the same parasite. Although the author protests his allegiance to the International Committee upon Zoological Nomenclature, he disregards the rules of that Committee, and indeed, revises the Latin language. He omits diphthongs not only when he uses the current simplified spelling of words derived from Latin, but also in proper generic and specific names. Thus *Amœba* becomes *Amœba*, and *Tænia* becomes *Tenia*—terms which have no validity under the rules of nomenclature. The embarrassing confusion of names given to one parasite is well illustrated by the different terms for the nematode "whip-worm," which the author scatters through the text. These are not grouped as synonyms under the valid designation, but occur as follows: *Trichocephalus*, p. 352, *Trichiuris*, p. 353, *Trichiuris trichiurus*, p. 358, *Trichiuris trichiuras*, p. 392, *Trichiuris trichiuris*, p. 449, *Trichocephalus trichiura*, p. 393, *Trichocephalus trichiuris*, p. 394, *Trichiuris trichiura*, p. 713.

Although the book bears the date 1920, there is little evidence to show that the author has kept up with recent work in this field. This is exhibited particularly in the section on the *Entamœbæ*. Dobell's work is not mentioned, while the fanciful conceptions of Schaudinn and Craig are repeated. *Entamœba histolytica* and *Entamœba tetragena* are described as distinct species, and their differences are set forth in a table. The use of emetine in the treatment of amœbic dysentery is not mentioned.

The section on the *Flagellata* is confused and inadequate. The spirochætes, however, are included in this section without hesitation. Their inclusion leads to this statement on p. 220: "Noguchi and Pareja claim to have found a flagellate in the blood of yellow fever patients." Undoubtedly, *Leptospira icteroides* is referred to here. The statement is, to say the least, misleading, since it has not been determined whether the spirochætes are bacteria or protozoa.

The chapters on Helminthology are the best in the book. Here also contradictions occur in the text. In the table opposite p. 242 the genital pore of *Schistosoma* is said to be anterior to the ventral sucker, whereas on p. 259 it is said to be posterior to it.

The descriptions and figures of the insects are excellent in some respects, but inadequate for the differentiation of species. Several errors and misleading statements quickly strike the attention of the reader. On p. 552, *Glossina palpalis* is said to transmit *Trypanosoma brucei*, and on p. 514 it is mentioned without conviction that the "louse has been said to transmit the virus of typhus fever."

A great variety of fungi, and bacteria, together with the technic of mycology, bacteriology, microscopy, hæmatology, and serology are described in the final 100 pages of the book. The futility of this sort of compressed compilation is shown by the description of the microscope, which is contained in a paragraph of 22 lines. The yeast-like organism *Monilia* is classed with the *Hyphomycetes* along with *Actinomyces* (which is incorrectly called *Discomyces*). Many of the laboratory procedures described are antiquated, and the directions given are too sketchy to be of value.

There are many excellent pictures in the book, and also many which are drawn to such a small scale that the details of the structures supposed to be represented cannot be seen. These are, therefore, of no assistance in the elucidation of a text which is often obscure.

It would be unprofitable to continue to catalogue the errors found in this book. Much correct information is contained in it, and the book may serve as a means of orientation in parasitology. But its authority is destroyed by its errors and omissions. It disappoints expectations and does not supply the need of a comprehensive and accurate text-book in English on the subject of Parasitology.

S.B-J.

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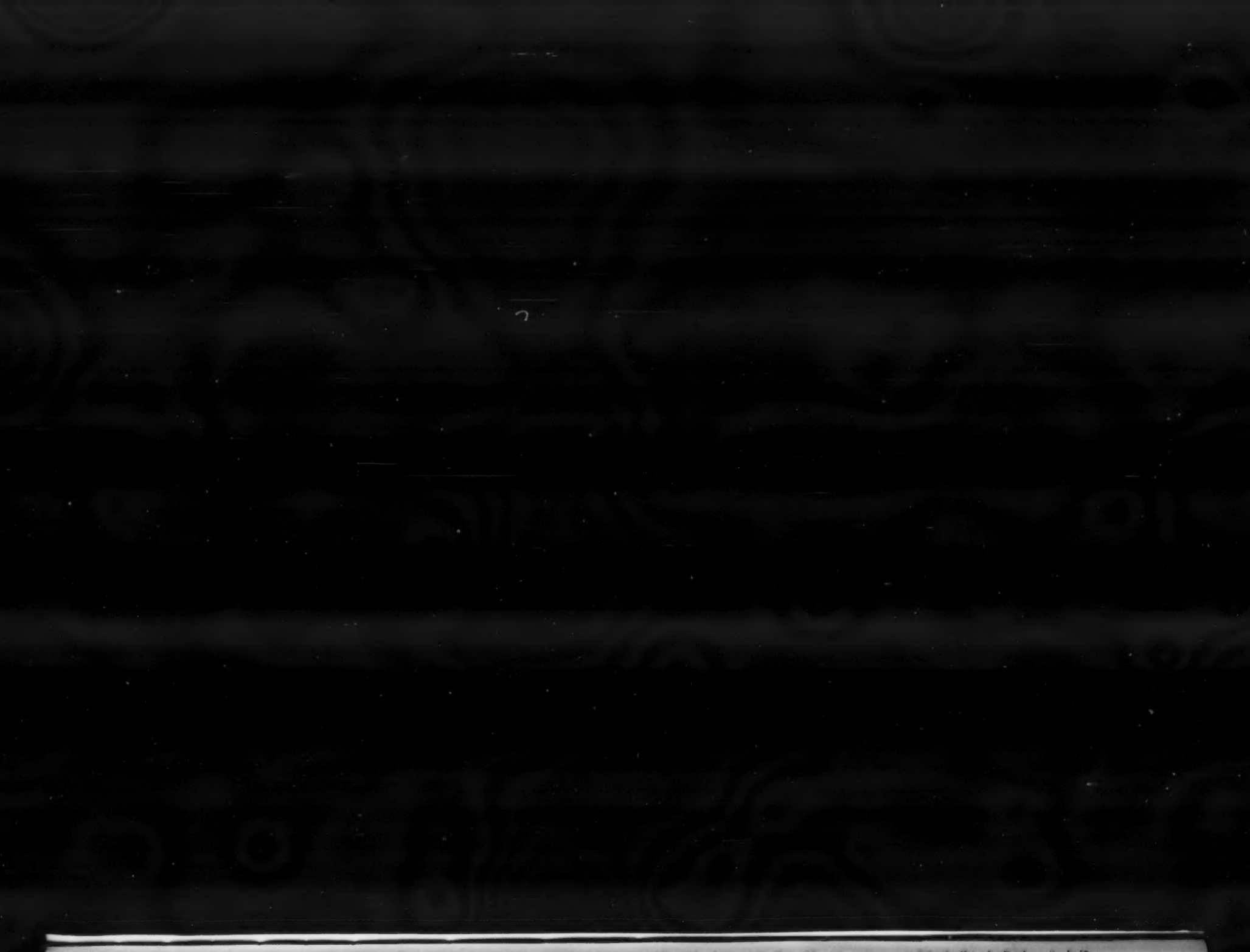
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